Cannabis and (endo)cannabinoid system

Thiravat Hemachudha,MD,FACP

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Thairath หมอดื้อ

what we know about cannabis and (endo) cannabinoid system

bonus role in thriving behavior

40 years back (2522 BE)

- *2014 by Prof. Pongkiat Kankirawatana,MD*

- I gave this grand round in 2014 prior to the Alabama state passed the law allowed us (UAB) doing the research on CBD treatment in epilepsy. It's old slides, not up to date but hopefully helpful to convince folks who do not believe in therapeutic benefit of cannabis.

- Between 2014 and 2016
- 2016 until now

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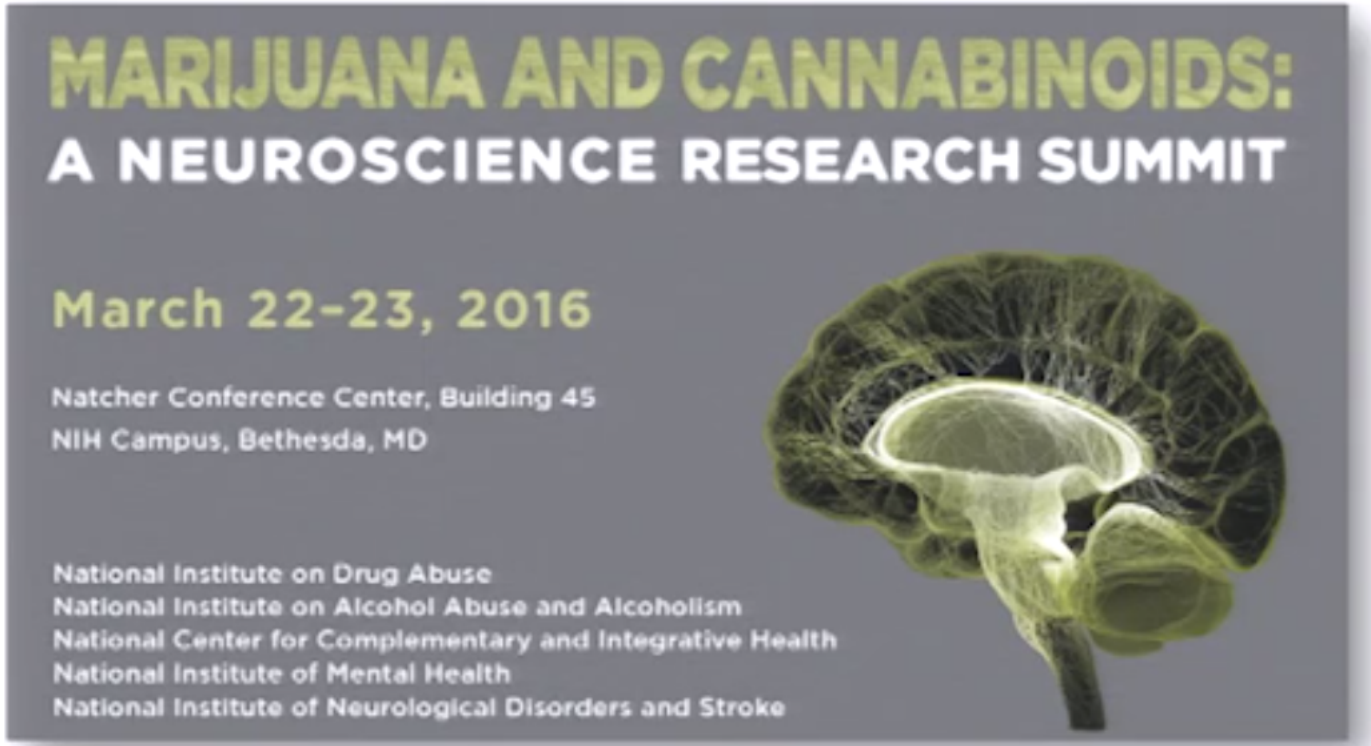
Prof. Pongkiat Kankirawatana, MD
2018 interview (VDO)


MARIJUANA AND CANNABINOIDS:
A NEUROSCIENCE RESEARCH SUMMIT
March 22-23, 2016
Natcher Conference Center, Building 45
NIH Campus, Bethesda, MD
National Institute on Drug Abuse
National Institute on Alcohol Abuse and Alcoholism
National Center for Complementary and Integrative Health
National Institute of Mental Health
National Institute of Neurological Disorders and Stroke
State of the Science of Cannabis Research:
Update from the NIH Marijuana Summit
Susan R.B. Weiss, PhD
Director
Division of Extramural Research
00:38
May 20, 2016
vimeo

International Journal of
Molecular Sciences

MDPI

Review

Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System

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Received: 9 February 2018; Accepted: 11 March 2018; Published: 13 March 2018


Collins, M.D., Ph.D., Director,
National Institutes of Health
NIH
National Institutes of Health

NIDAnews
@NIDAnews

Following

.@ONDCP Director @Botticelli44 : "Drug policy needs to be dictated by science."
#MJNeuroSummit

17 14

7:22 PM - 22 Mar 2016

NIH
National Institute on Drug Abuse

NIDAnews
@NIDAnews

NIDA's mission is to advance science on the causes and consequences of drug use and addiction. Comment policy: 1.usa.gov/GFdwOz #AddictionScience

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Milestones in Cannabinoid Pharmacology

- 1964 D^9-THC synthesized and structure identified (Gaoni & Mechoulam)
- 1980s Synthetic cannabinoids
- 1988 - Cannabinoid-binding sites in rat brains identified (Devane et al.)
- 1991 - Human cannabinoid receptor CB_1 cloned (Matsuda et al.)
- 1992 CB_2 receptor (Kaminski et al.)
- 1992 - Discovery of the first endocannabinoid, arachidonoyl ethanolamide, later named anandamide (Devane et al. in porcine brain)
- 1993 - Peripheral CB2 receptor cloned (Munro et al.)
- 1995 - Discovery of the 2^{nd} endocannabinoid, 2-arachidonoyl glycerol (2-AG) (Mechoulam, Sigiura, et al)
- 1994-7 Receptor antagonists (Rinaldi-Carmona et al.)
- 1998 Endogenous ligands shown to be analgesic (Walker et al.))
- 1998 CB_1 receptor “knock out” mice (Ledent et al. , Zimmer al.)
- 2000 CB_2 receptor “knock out” mice (Buckley et al.)
- 2001 Noladin -ether identified
- 2001+ Synthetic cannabinoids, more on the endogenous system, biosynthesis and degradation, delivery systems etc.

Endocannabinoid

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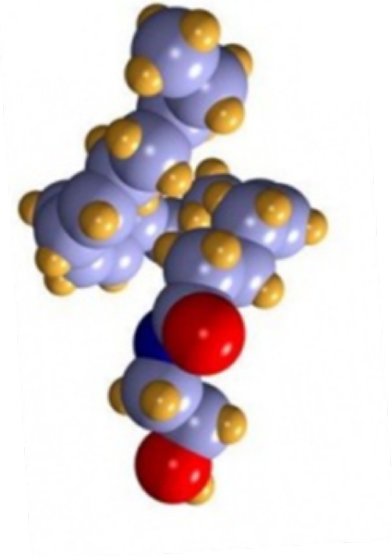
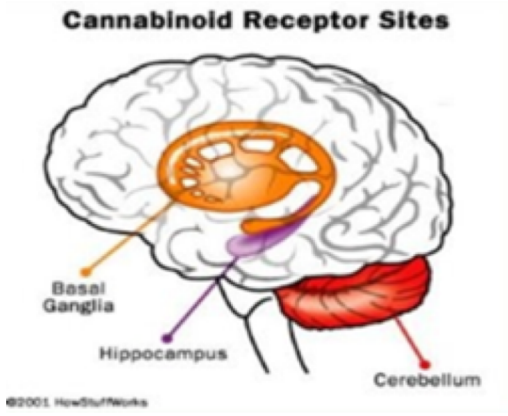
- 28yrs after discovering THC, in 1992, Dr. Mechoulam, Dr. William Devane and Dr. Lumir Hanus, identified the brain's first endogenous cannabinoid (or endocannabinoid) - the brain's natural version of THC -which they called 'Anandamide,' from the Sanskrit word 'ananda,' (means 'eternal bliss' or 'supreme joy.
- ECS is a group of neuromodulatory lipids and their receptors in the brain that are involved in a variety of physiological processes including appetite, pain-sensation, mood, and memory;
- It mediates the psychoactive effects of cannabis
- Vigorous exercise stimulates the release of anandamide, and the sense of euphoric well-being that comes with a healthy workout





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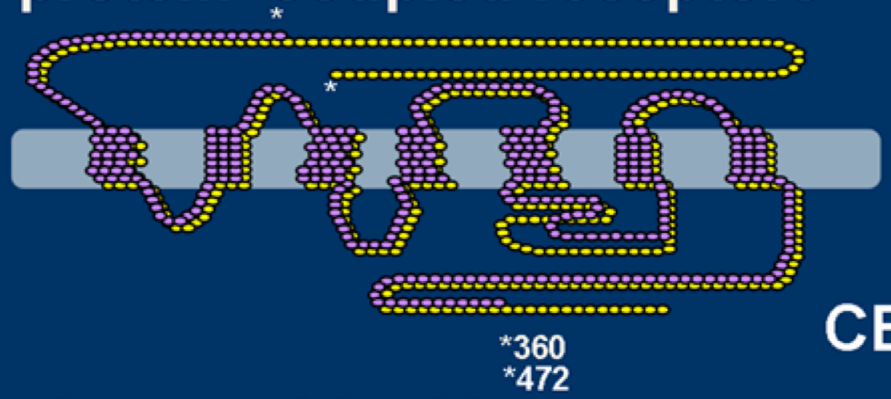
Key ECS Elements

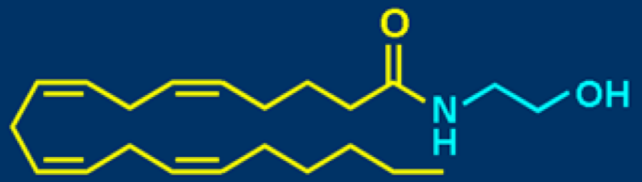
Cannabinoid receptors are G-protein–coupled receptors



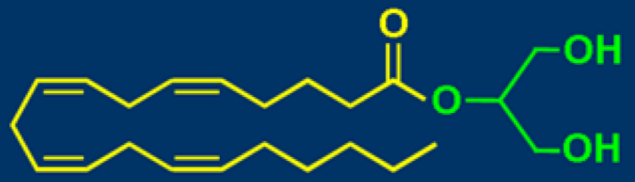
CB_1 receptor

- Central nervous system
  - Hippocampus
  - Basal ganglia
  - Cortex
  - Cerebellum
  - Hypothalamus
  - Limbic structures
  - Brainstem
- GI tract (myenteric neurons and epithelial cells)
- Liver (hepatocytes)
- Adipose tissue
- Muscle
- Pancreas (α-cells)

Endocannabinoids



Anandamide



2-Arachidonoyl-glycerol

Endogenous, phospholipid-derived metabolites that bind to and activate cannabinoid receptors

De Petrocellis et al. *Br J Pharmacol*. 2004;;141:765-774.
Pertwee et al. *Pharmacol Ther*. 1997;74:129-180.
Roche R et al. *Histochem Cell Biol*. 2006;126(2):177-187.

CB_2 receptor

- Immune cells and tissues
  - T cells, B cells
  - Macrophages
  - Dendritic cells
  - Spleen, tonsils
  - Adipose tissue

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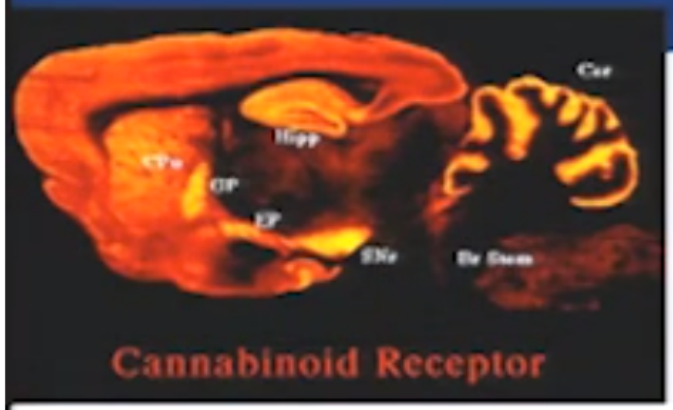
Physiological Effects of Endocannabinoids

- Endocannabinoids are often produced as an adaptive response to cellular stress, aimed at reestablishing cell homeostasis
- Endocannabinoids affect a large number of physiologic processes including
  - –Feeding behavior
  - –Energy balance, metabolism, and GI function
  - –Pain perception
  - –Motor control and posture
  - – Learning, memory, and emotions
  - – Immune and inflammatory responses
  - – Cardiovascular function
  - – Reproduction
  - – Bone formation

Cota D, Woods S. *Curr Opin Endocrinol Diabetes*. 2005;12:338-351; De Petrocellis L et al. *Br J Pharmacol*. 2004;141:765-774; Pagotto Uet al. *Endocr Rev*. 2006;27:73-100; Ameri A. *Prog Neurobiol*. 1999;58:315-348; Cota Det al. *J Clin Invest*. 2003;112:423-431; Di Marzo V, Matias I. *Nat Neurosci*. 2005;8:585-589; Kershaw EE, Flier JS. *J Clin Endocrinol Metab*. 2004;89:2548-2556; Correa F et al. *Mini Rev Med Chem*. 2005;5:671-675; van der Stelt M et al. *Embo J*. 2005;24:3026-3037; Wang H et al. *Endocr Rev*. 2006;27:427-448; Idris AI et al. *Nat Med*. 2005;11:774-779; de Oliveira Alvares L et al. *Brain Res*. 2006;1075:60-67; Arenos JD et al. *Eur J Pharmacol*. 2006;539:177-183; Mikics E et al. *Behav Pharmacol*. 2006;17:223-230; Guindon J et al. *Pain*. 2006;121:85-93.

Cannabinoid Receptors Are Located Throughout the Brain

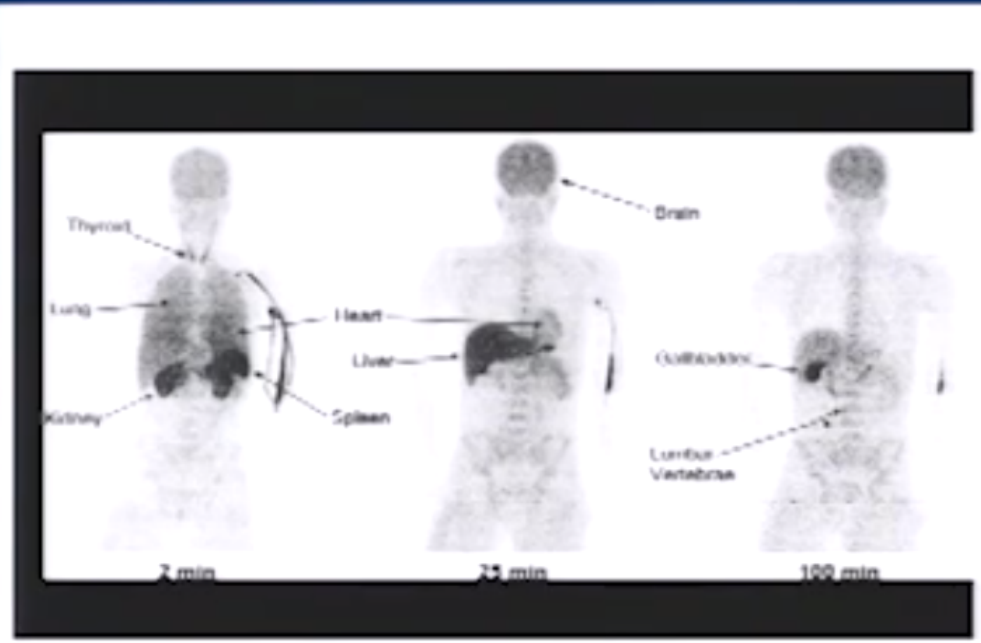


Regulation of:

- Brain Development
- Memory and Cognition
- Movement Coordination
- Pain Regulation & Analgesia
- Immunological Function
- Appetite
- Motivational Systems & Reward

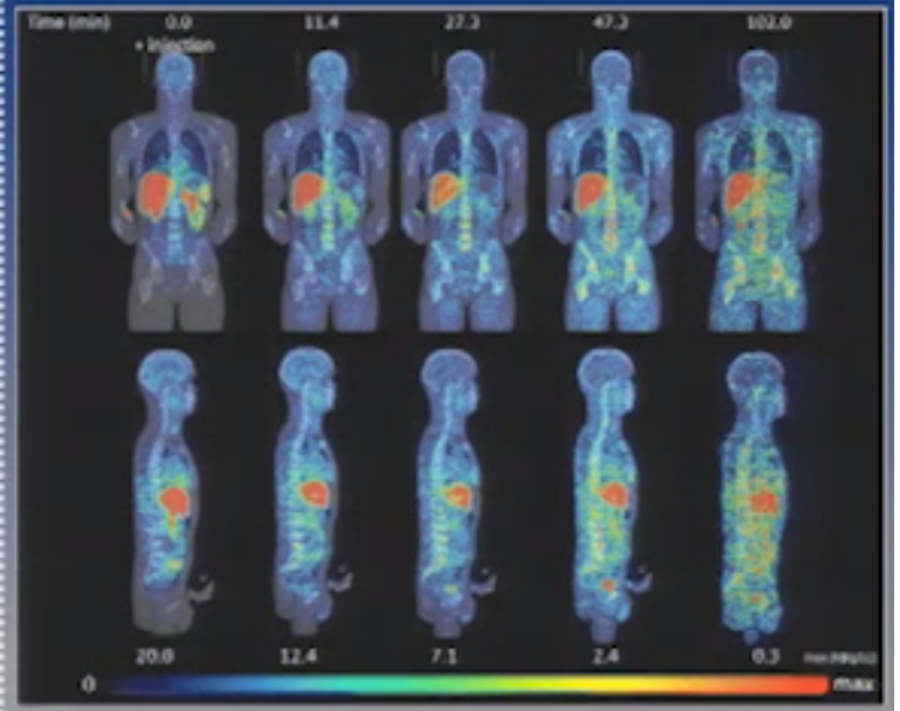
Cannabinoid Receptors Are Also Located Throughout the Body

Whole Body Distribution of CB1 Receptors (2, 25, and 100 min after injection of 11C-MePPEP)



Terry et al., Eur J Nucl Med Mol Imaging. 2010

PET images of [11C]-NE40 (CB2R radioligand)



Ahmad et al., Mol Imaging Biol. 2013 A

The neuropsychopharmacology of cannabis: a review of human imaging studies

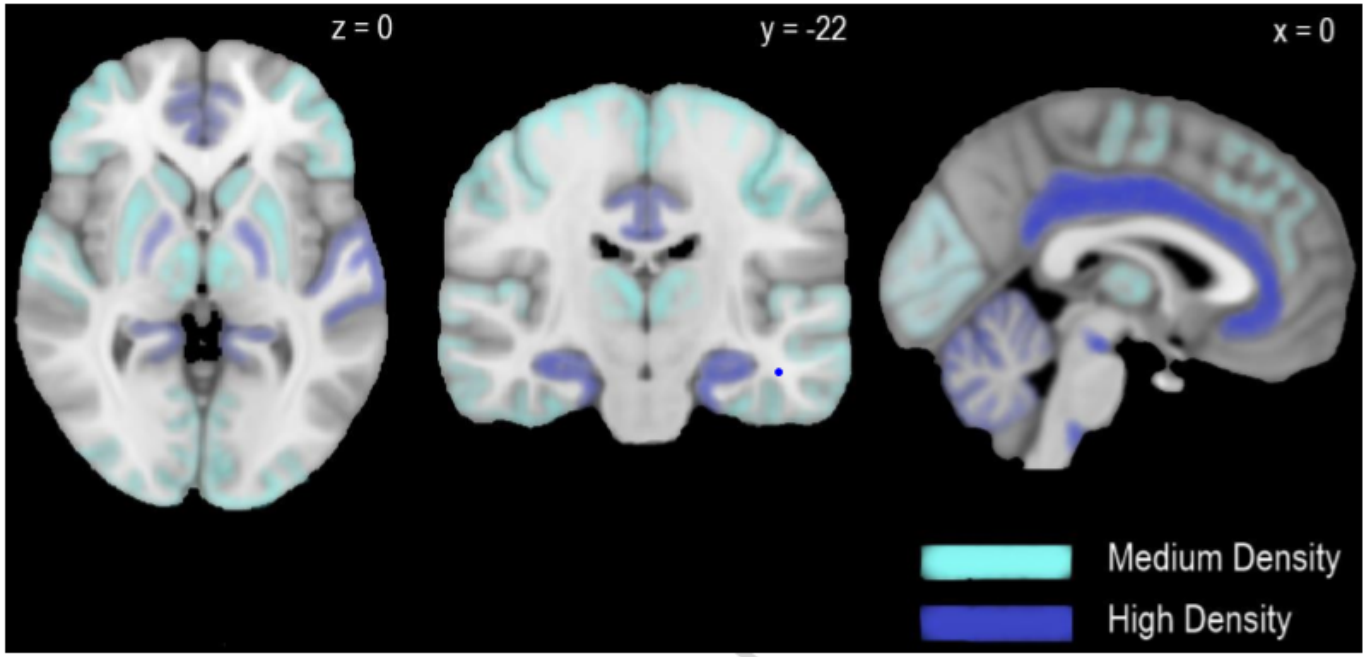
*Michael A. P. Bloomfield [1,2,3,4,5], Chandni Hindocha[1,2,4], Sebastian F. Green[1], Matthew B. Wall[2,6,7], Rachel Lees[1,2,8], Katherine Petrilli[1,2,8], Harry Costello[1], M. Olabisi Ogunbiyi[1], Matt G. Bossong[9], Tom P. Freeman[2,10,11]

Endocannabinoids are fatty-acid cannabinoids produced naturally in the body (anandamide and 2-AG).

Phytocannabinoids are concentrated in the oil resin of cannabis buds and leaves (THC and CBD) with over 100 identified in the cannabis plant.

Synthetic cannabinoids are manufactured artificially in a laboratory to mimic the effects of natural cannabinoids.

Figure 1: The distribution of CB_1Rs across the human brain.



These axial (left), coronal (middle) and sagittal (right) views schematically depict regions of medium and high endocannabinoid type 1 receptor (CB_1R) concentration. This was extrapolated from mean labelling densities as described by Glass *et al*. (1997). [^{3}H]CPP55,940 binding >80 fmol/mg was defined as high and 40-80 fmol/mg was defined as medium. Regions with high CB_1R concentration include (in alphabetical order): amygdala (not in view), cerebellum, cingulate gyrus, dorsal motor nucleus of the vagus, entorhinal cortex, globus pallidus, hippocampal formation, middle frontal gyrus, substantia nigra, and Wernicke's area. Regions with medium CB_1R concentration include (in alphabetical order): auditory cortex (right), caudate nucleus, mediodorsal nucleus of the thalamus, motor cortex, occipitotemporal gyrus, putamen, somatosensory cortex, and visual cortex. Montreal Neurological Institute coordinates (x,y,z) are shown above.

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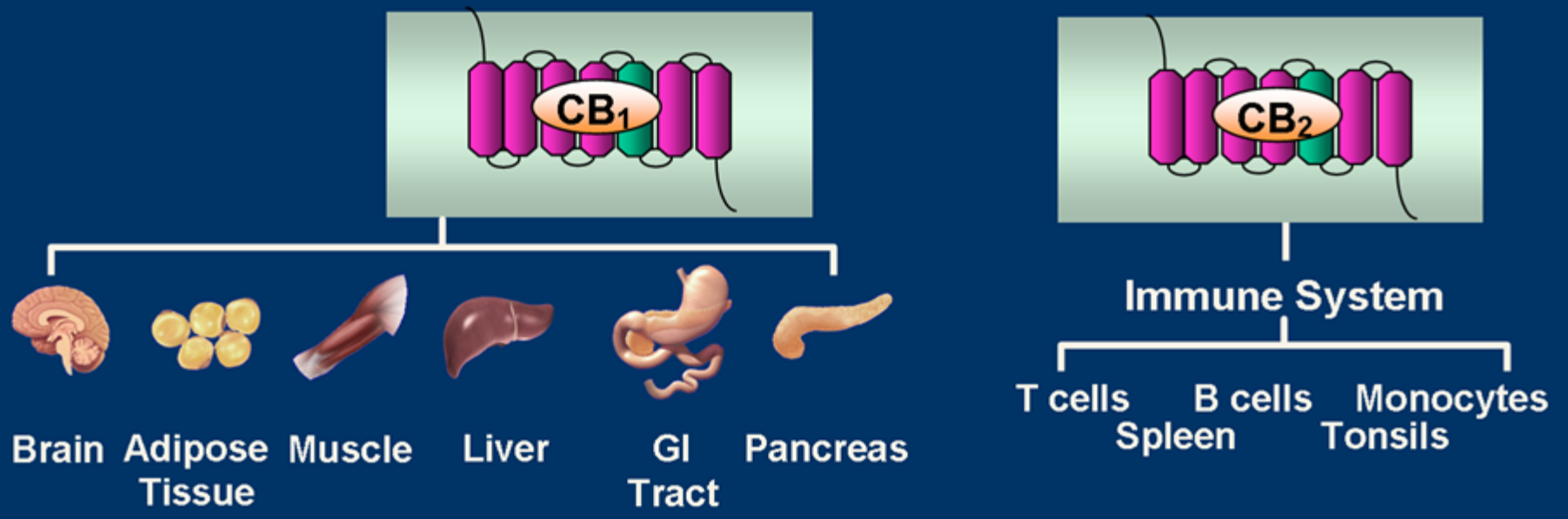
Cannabinoid Receptors



- G-protein–coupled receptors
- CB_1 receptors highly expressed in the brain
  - CB_1 receptors also found in adipose tissue, liver, muscle, the gastrointestinal tract, pancreas, as well as reproductive and cardiovascular tissues
- CB_2 receptors are expressed primarily in immune cells
  - CB_2 receptor expression in neurons is being studied

Devane WA et al. *Mol Pharmacol*. 1988;34:605-613.
Munro S et al. *Nature*. 1993;365:61-65.
Ameri A. *Prog Neurobiol*. 1999;58:315-348.
Osei-Hyiaman D, DePetrillo M, Pacher P, et al. *J Clin Invest*. 2005;115:1298-1305.
Cota D, Woods SC. *Curr Opin Endocrinol Diabetes*. 2005;12:338-351.

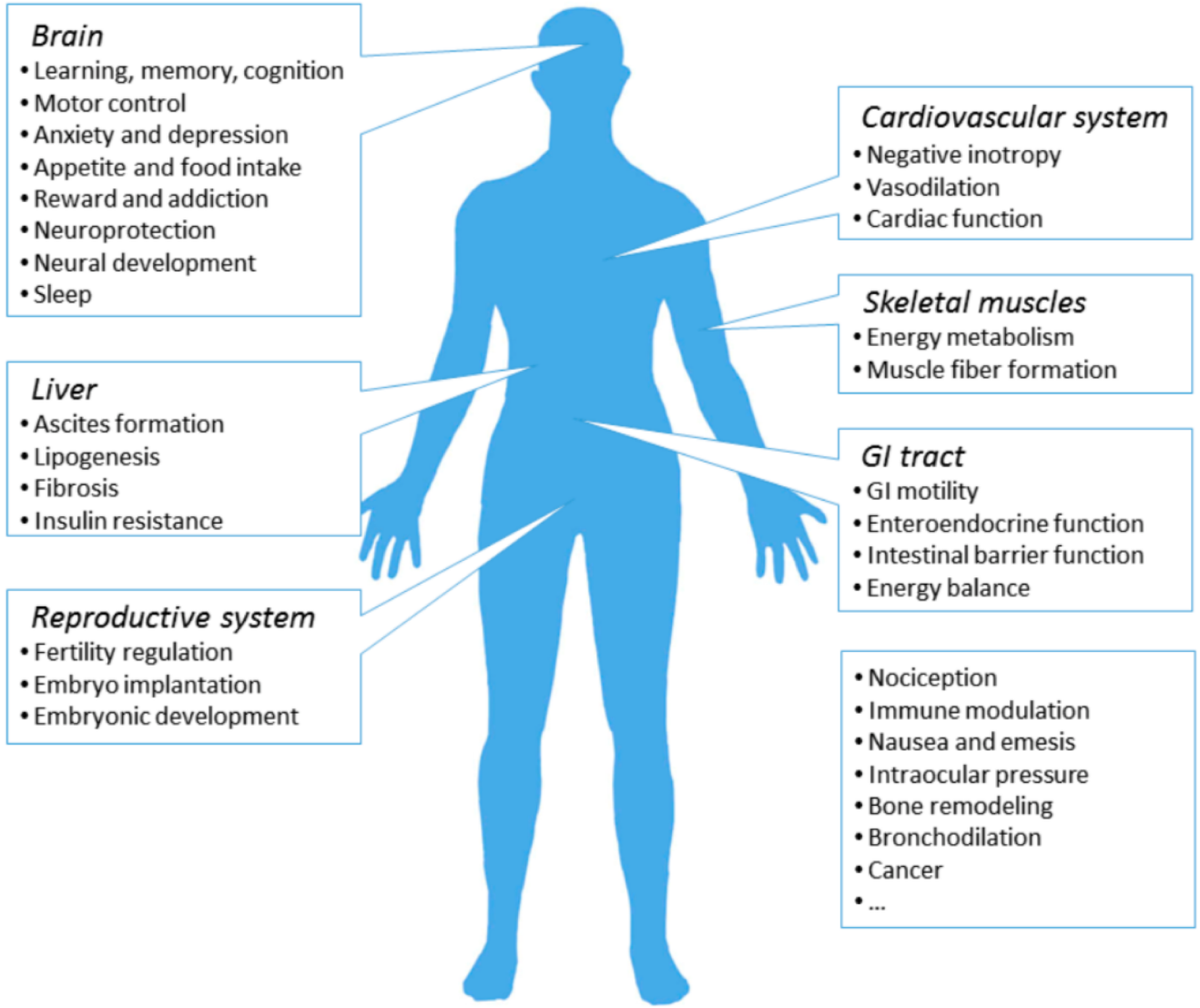
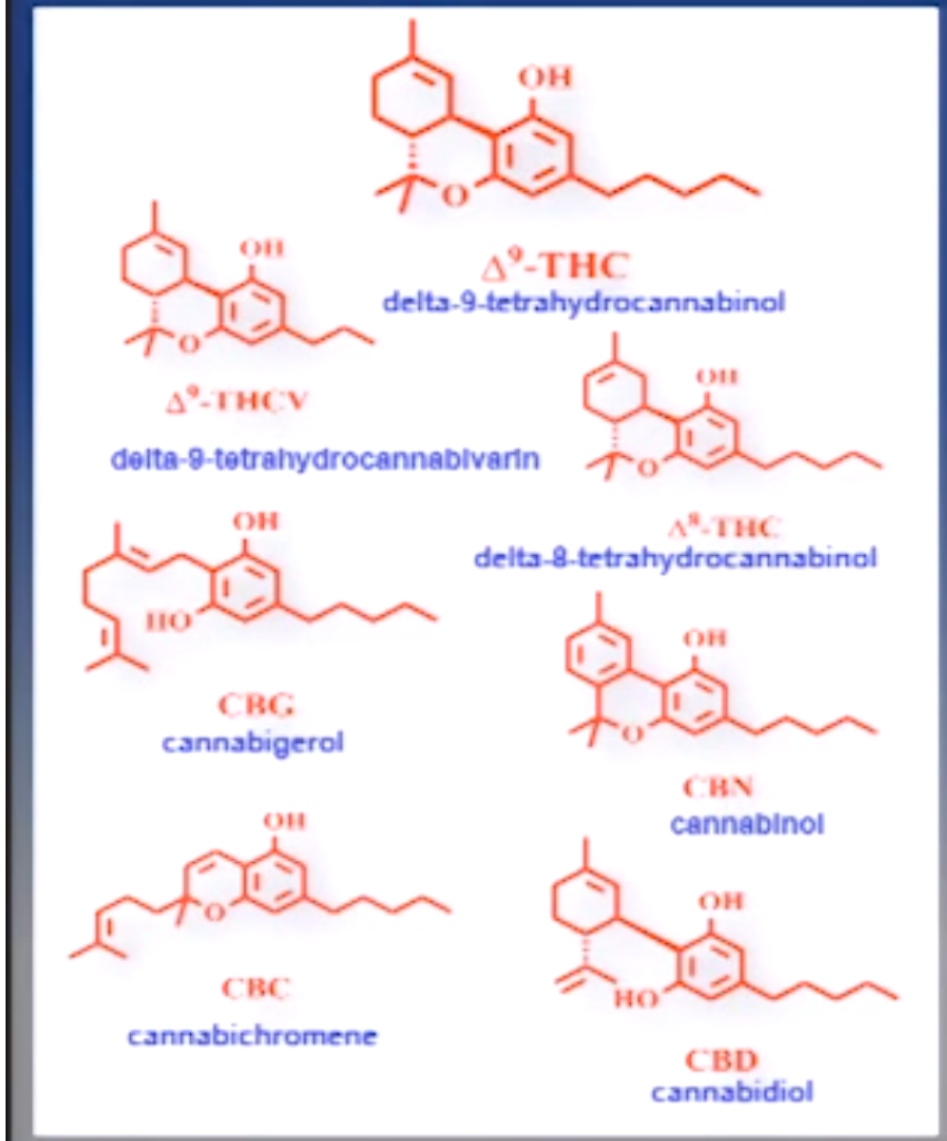


Figure 2. Major localization sites and associated functions of the CB1R in the human body. The majority of CB1Rs expressed in human body is found in the brain, where it is involved in various neurological activities. CB1Rs on the peripheral sites, although to a lesser extent, participates in the regulation of local tissue functions.

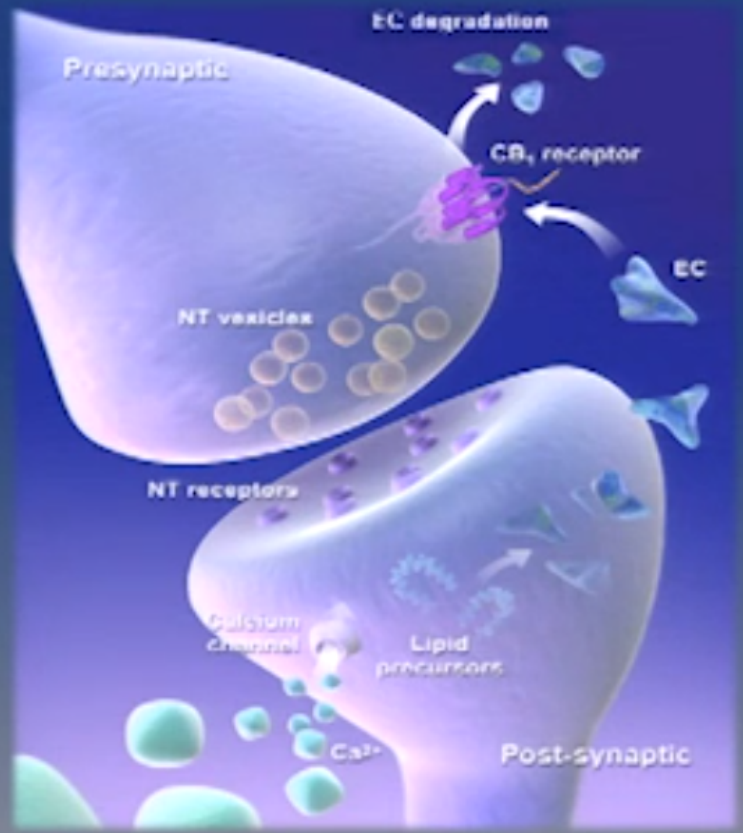
Exploiting the Cannabinoid System for Therapeutic Purposes

- Exogenous compounds
  - Phytocannabinoids
    - THC, CBD, combinations
  - Synthetic cannabinoids
    - Dronabinol
- Endogenous manipulation
  - FAAH inhibitors
  - MAGL inhibitors
  - Allosteric modulators
- Receptor targets
  - CB1, CB2, TRPV1, PPAR, 5-HT, peripheral, others…

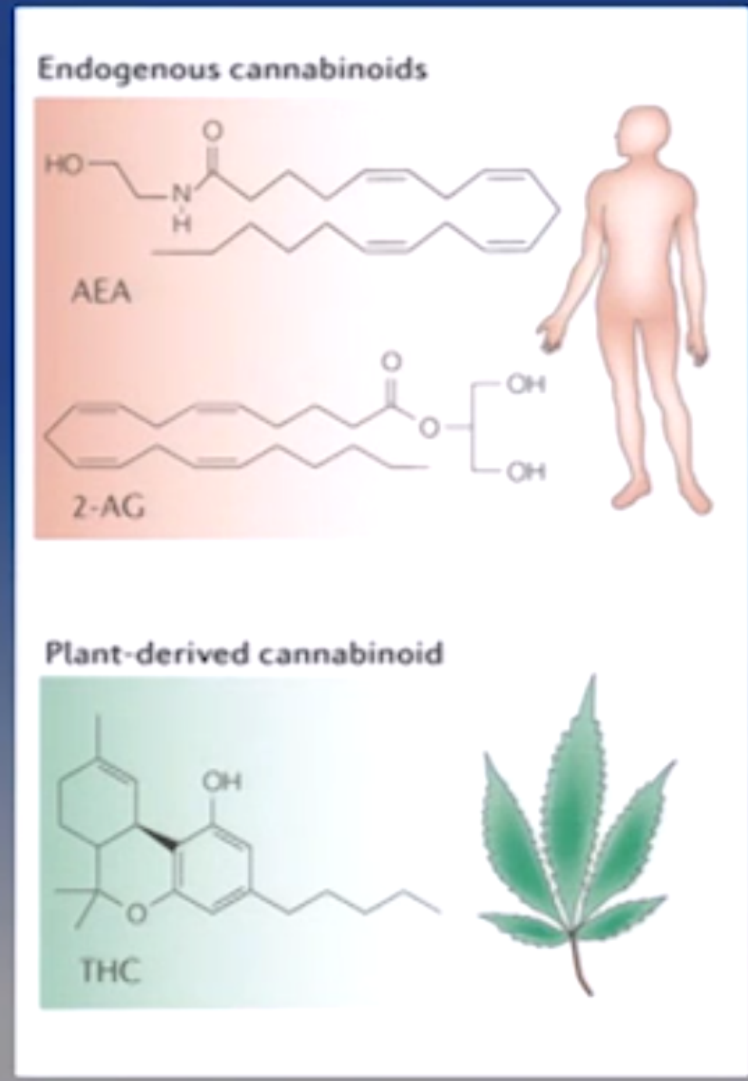
Marijuana contains ~100 cannabinoids plus other chemicals in varying concentrations



Mechanism of Action of Cannabinoids



Endocannabinoids are produced *on demand*. They travel back to the transmitting neuron to dampen further activity.



Source: Mackie K. Ann Rev Pharmacol Toxicol., 2006

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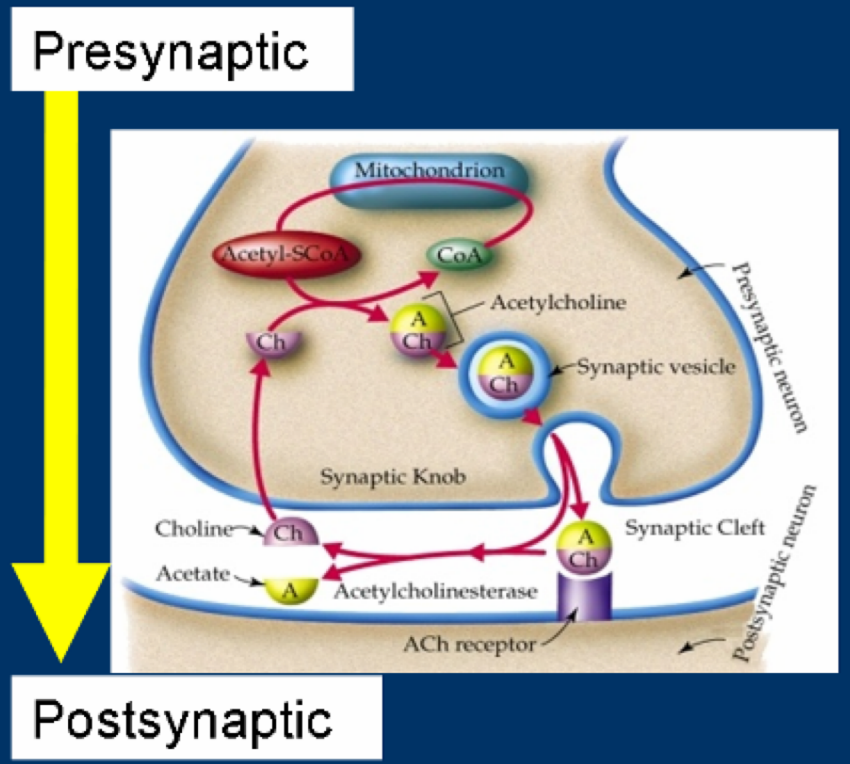
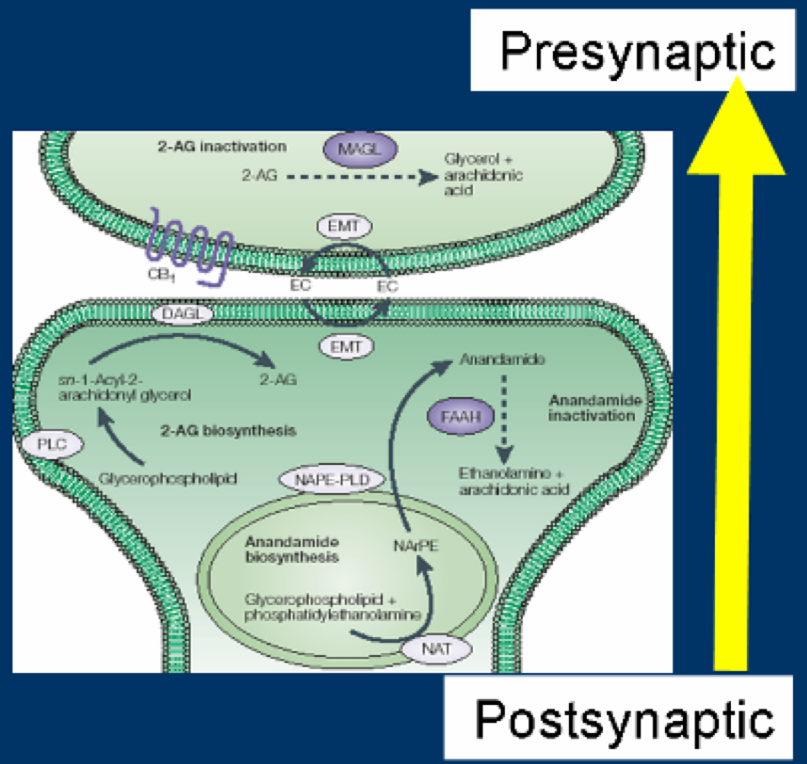
Difference Between Classical and Retrograde Neurotransmission

Classical neurotransmitter



Retrograde neurotransmitter



Di Marzo V, Matias I. *Nat Neurosci*. 2005;8:585-589.
Di Marzo Vet al. *Nat Rev Drug Discov*. 2004;3:771-784.
Wilson RI, Nicoll RA. *Nature*. 2001;410:588-592.
Vaughan CW, Christie MJ. 2005:367-383.

ENDOCANNABINOID SYNAPTIC TRANSMISSION

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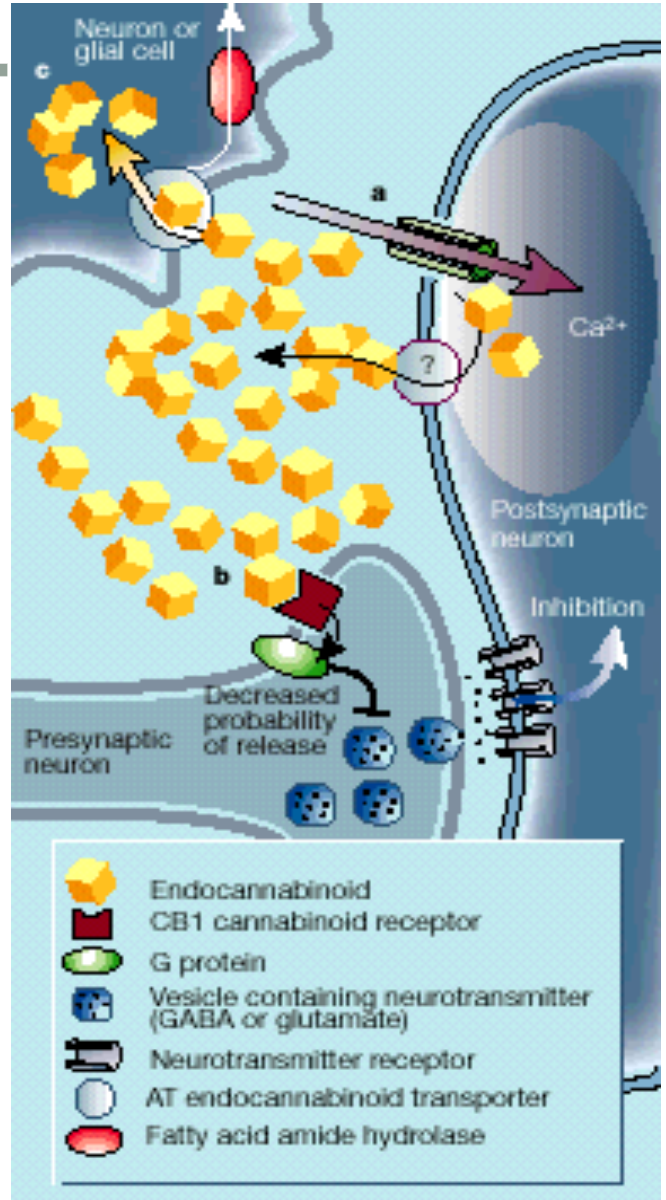

- Typically released by principal cells in response to prolonged depolarization, act as retrograde messengers to inhibit synaptic transmission
- Excitatory neurotransmitter (eg.glutamate) causes an influx of Ca^{++} into the post-synaptic neuron.
- The presence of Ca^{++} post-synaptically causes the production of endocannabinoids in the post-synaptic neuron.
- Endocannabinoid is then released into the synaptic cleft
- In the synaptic cleft the endocannabinoid binds to the Cannabinoid Receptor of the pre-synaptic neuron
- This in turn modulates neurotransmission pre-synaptically
- *Post-Synaptic Neuron → Pre-Synaptic Neuron (Renegade Transmission or Retrograde Transmission)*

(Wilson & Nicoll, 2001; Ohno-Shosaku et al., 2001; Kreitzer & Regehr, 2001)

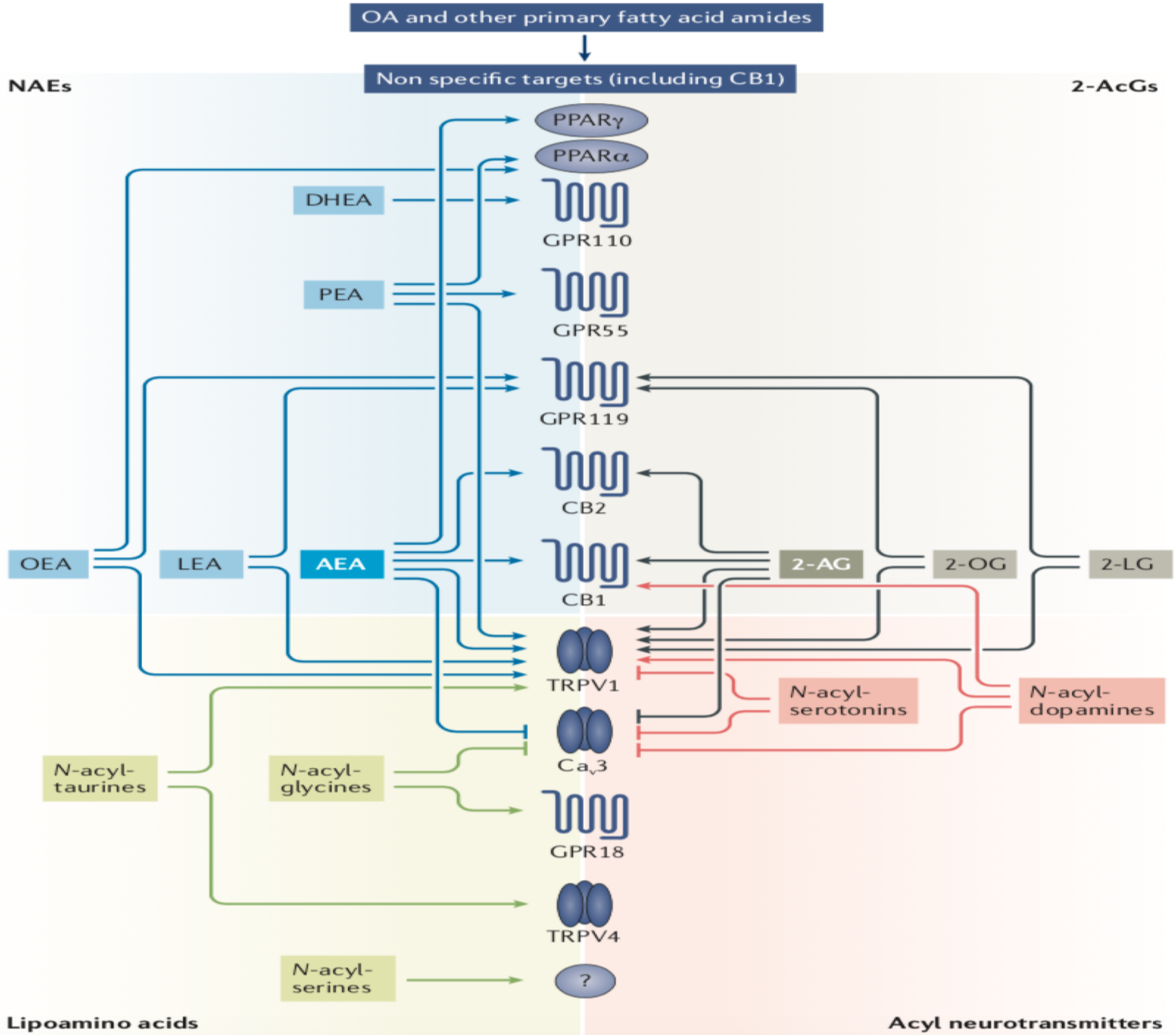

Figure 1 | **Endocannabinoidome mediators and receptors.** The main endocannabinoids, *N*-arachidonoyl-ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), are part of larger families of lipids, the *N*-acylethanolamines (NAEs) and the 2-acylglycerols (2-AcGs), respectively. Numerous other members of these families signal through other G protein-coupled receptors (GPCRs), ion channels and nuclear receptors, as shown. In addition, long-chain primary fatty acid amides, lipoamino acids and acyl neurotransmitters signal through some of the receptors used by NAEs and 2-AcGs. 2-LG, 2-linoleoyl glycerol; 2-OG, 2-oleoyl glycerol; Ca_v3, T-type Ca^{2+} channel; CB, cannabinoid receptor; DHEA, *N*-docosahexaenoyl ethanolamine; GPR18, G protein-coupled receptor 18; LEA, *N*-linoleoyl ethanolamine; OA, oleamide; OEA, *N*-oleoylethanolamine; PEA, *N*-palmitoylethanolamine; PPAR, peroxisome proliferator-activated receptor; TRPV1, transient receptor potential cation channel subfamily V member 1.

Endocannabinoid system (ECS): Overview

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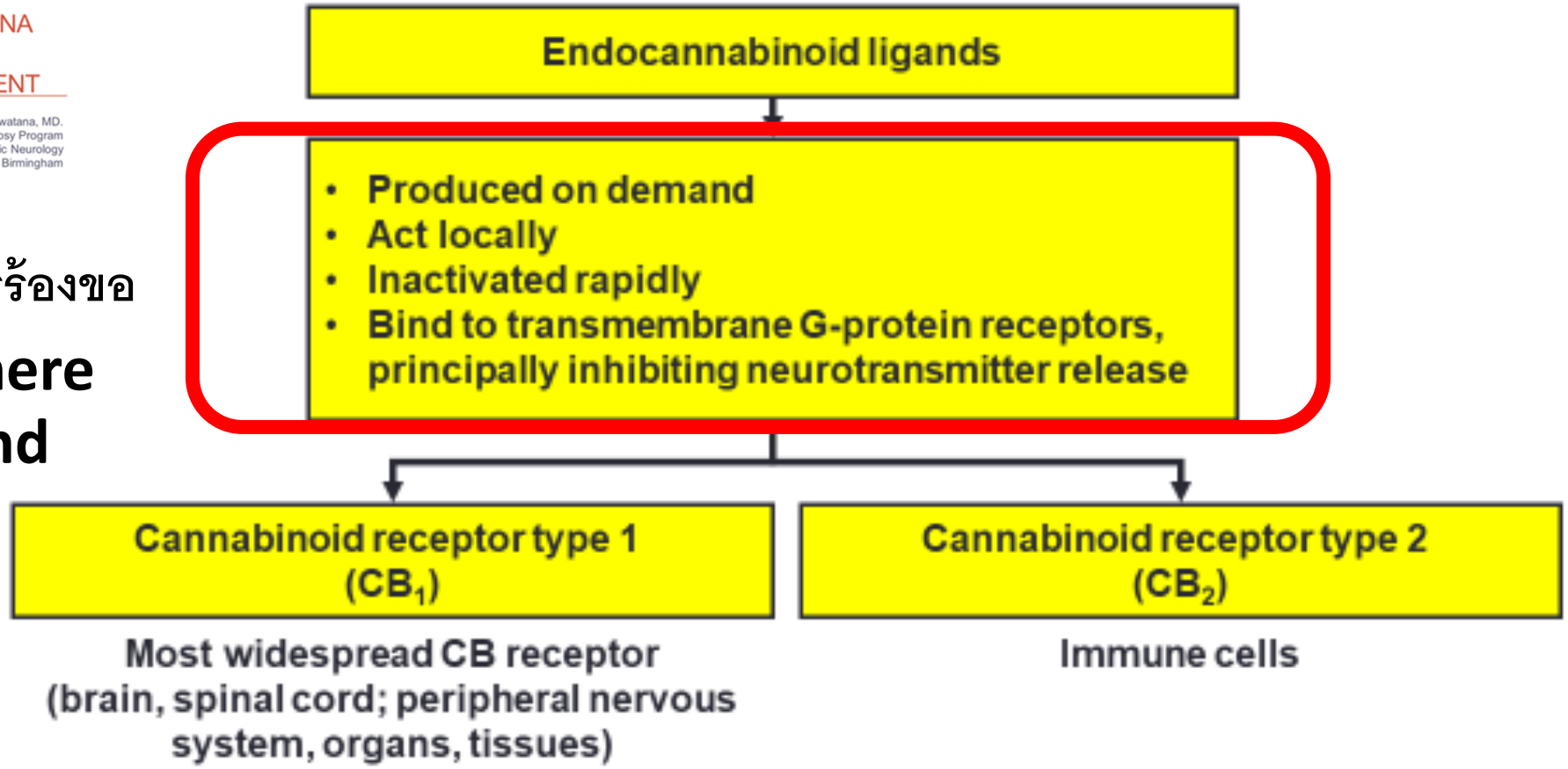
ผลิตเมื่อมีการร้องขอ

When/where
On demand

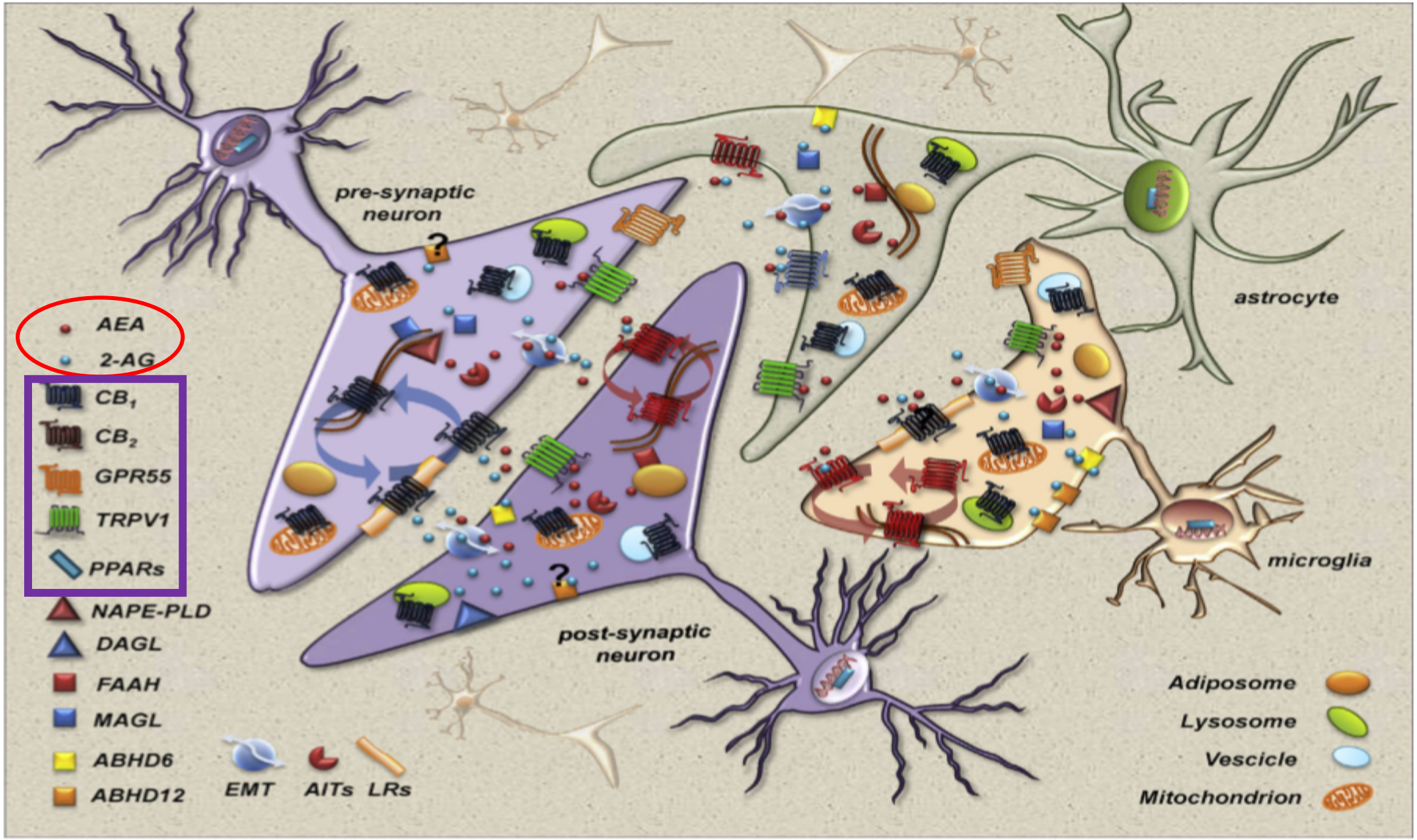
ปรับสมดุลย์



Gelfand EV, Cannon CP. *J Am Coll Cardiol*. 2006;47:1919-26.
Pagotto U et al. *Ann Med*. 2005;37:270-5.

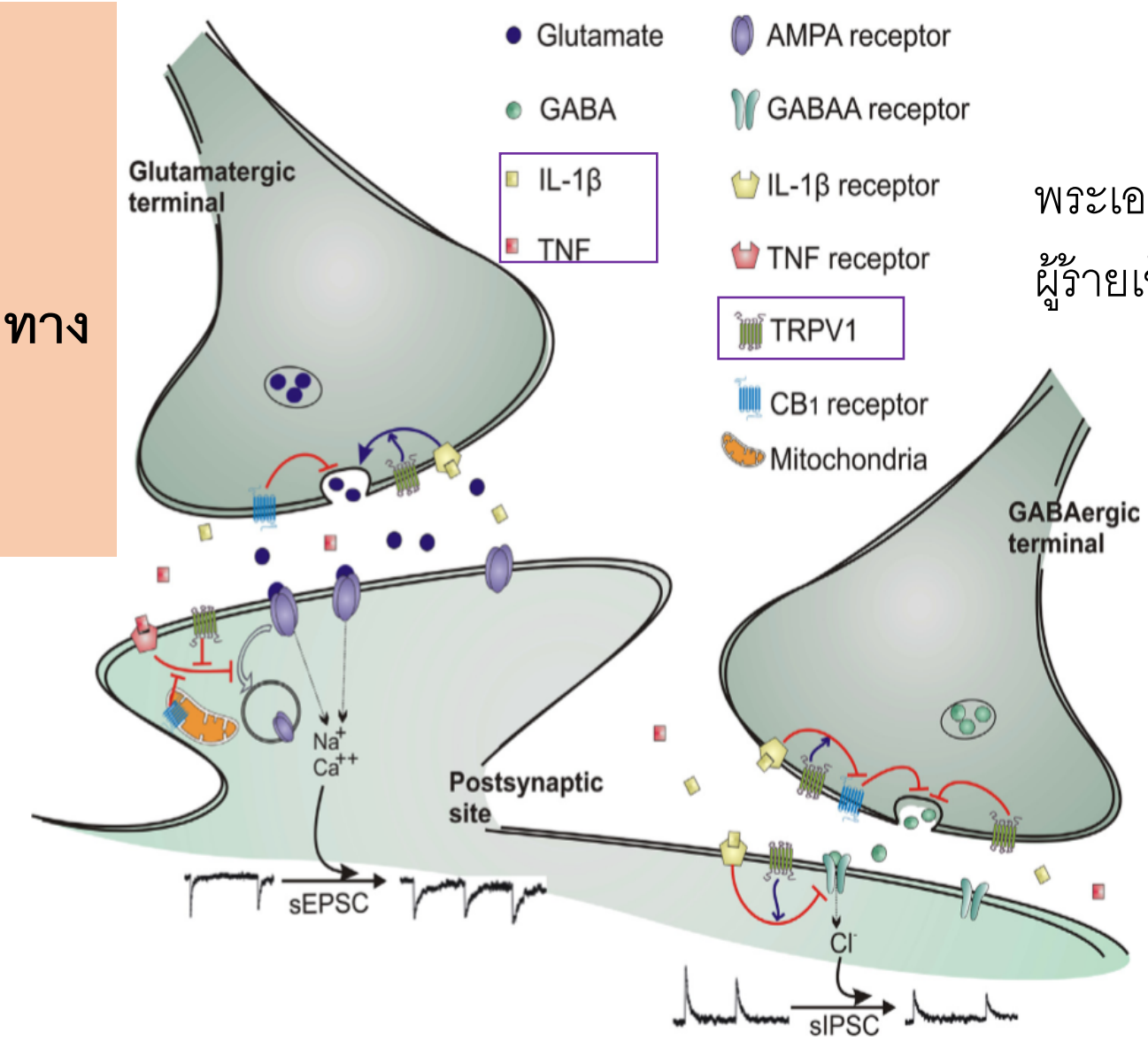
ECS overview

- on demand
- in a cell-specific
- and time-specific manner during pathological states to exert a homeostatic function


pre-synaptic neuron
post-synaptic neuron
astrocyte
microglia
AEA
2-AG
CB1
CB2
GPR55
TRPV1
PPARs
NAPE-PLD
DAGL
FAAH
MAGL
ABHD6
ABHD12
EMT
AITs
LRs
Adiposome
Lysosome
Vescicle
Mitochondrion

ระบบ **e cannabinoid**
ต่อต้านการอักเสบที่เกิดจาก
สาร **IL 1beta TNF**
ซึ่งจะเหนี่ยวนำ สารสื่อประสาทในทาง
เลว และต้านตัวดี

Receptor at where and of which system?



พระเอกเป็นผู้ร้าย
ผู้ร้ายเข้าพวกกับพระเอก

Fig. 4. Overall scheme of the presynaptic and postsynaptic perturbations mediated by proinflammatory cytokines and modulated by eCB system in EAE. IL-1β increases glutamate release at presynaptic terminals and TNF induces AMPA receptor upregulation, resulting in enhanced glutamate transmission. CB_1 contrasts the effects of IL-1β by reducing the frequency of spontaneous glutamate-mediated synaptic currents on presynaptic terminals, conversely TRPV1 is permissive for IL-1β synaptic effects on glutamate transmission. At the postsynaptic site, both CB_1 and TRPV1 restrain TNF-mediated potentiation on postsynaptic AMPA receptor. Moreover, IL-1β promotes the inhibition of CB_1 function on GABAergic synapses, thus mitigating the reduction of GABA release. Moreover, IL-1β reduces postsynaptic GABAA receptor function by promoting the decrease of GABA signaling. Finally, TRPV1 channels are permissive for IL-1β synaptic effects at both pre- and postsynaptic sites.

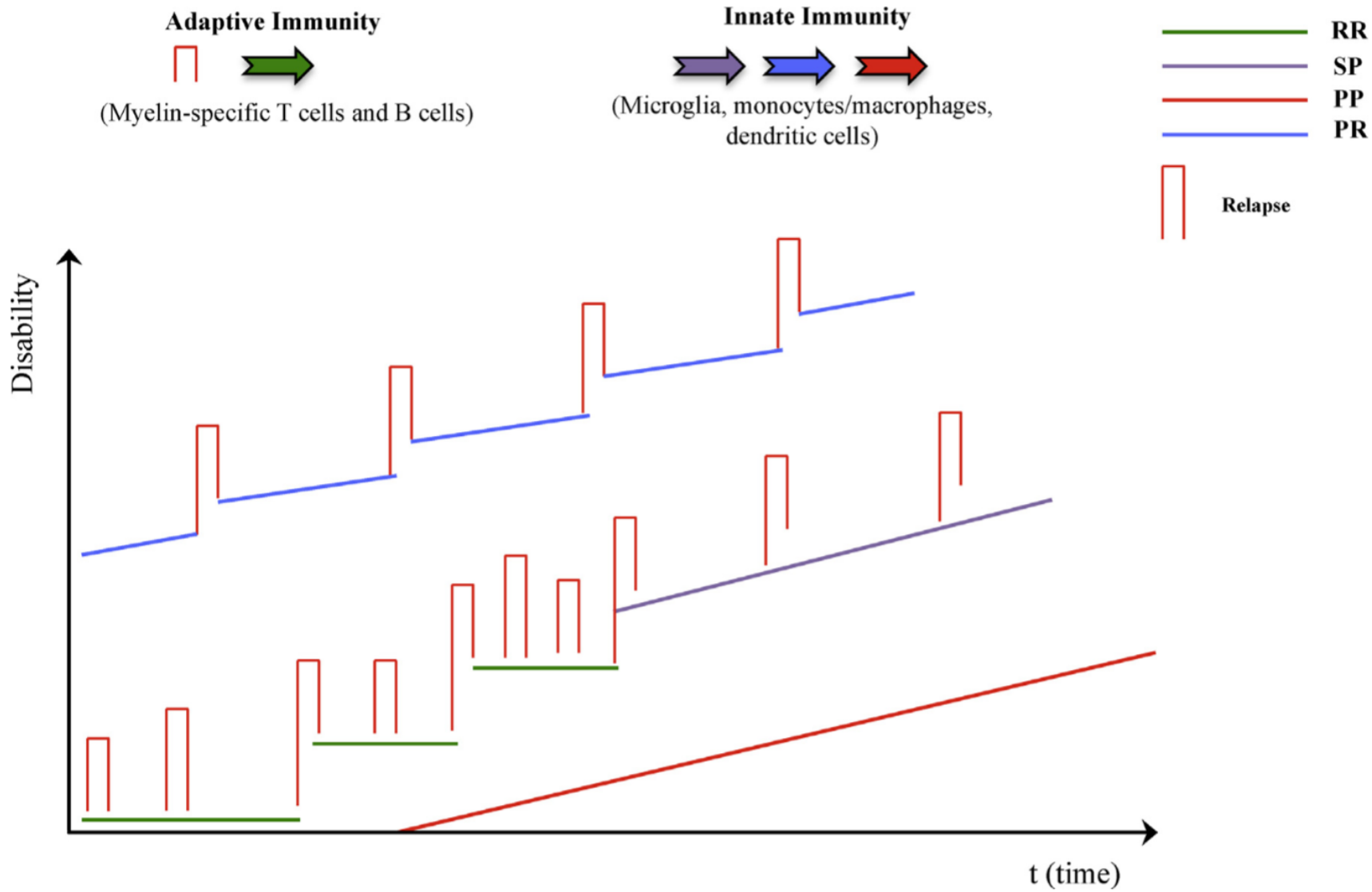


Fig. 1. The immunological basis of the different clinical forms of MS.

ลักษณะการดำเนินโรคสะท้อนถึงกลไกของระบบภูมิคุ้มกันที่ผิดปกติ เกิดการอักเสบจากกระบวนการแบบต้นและปลาย และมีผลกระทบต่อโครงสร้างของสมองในที่เปลือกหรือแกนประสาท รวมทั้งเหนี่ยวนำให้เซลล์ในสมองทำตัวเป็นศัตรู

Table 2
Alterations of distinct elements of the eCB system, and their role in inflammation and neurodegeneration in MS.

ECS element	Model	Sample	Variation	Effects	Reference
AEA	Chronic EAE	Brain, spinal cord	↑	Early inhibition of spasticity	Baker et al. (2001)
	Lewis EAE rats	Brain	↓	Worsening of disease development and neurological impairment	Cabranes et al. (2005)
	RR-MS	Autopsied brain	↑	Microglia-induced neuroprotection	Eljaschewitsch et al. (2006)
	EAE and RR-MS patients	Brain, CSF, plasma, T cells	↑	Neuroprotection	Centonze et al. (2007a)
	RR-MS, SP-MS	CSF	↓	–	Di Filippo et al. (2008)
	RR-MS, PP-MP, SP-MS	Plasma	↑	Disease progression	Jean-Gilles et al. (2009)
	RR-MS	T cells, B cells, NK cells	↑	–	Sánchez López et al. (2015)
NAPE-PLD/ FAAH	EAE and RR-MS patients	Brain, CSF, plasma, T cells	↑ NAPE-PLD and ↓FAAH	Neuroprotection	Centonze et al. (2007a)
	SP-MS	Plasma	↓FAAH	Disease progression	Jean-Gilles et al. (2009)
	RR-MS	mDC and pDC	↓FAAH in mDC and ↑ in pDC	Lack of immunoregulation	Chiurchiù et al. (2013)
	RR-MS	T cells, B cells, NK cells	←→	–	Sánchez López et al. (2015)
2-AG	Chronic EAE	Brain, spinal cord	↑	Late inhibition of spasticity	Baker et al. (2001)
	Lewis EAE rats	Brain	↓	Worsening of disease development and neurological impairment	Cabranes et al. (2005)
	RR-MS patients	CSF	←→	–	Centonze et al. (2007a)
	RR-MS, SP-MS	CSF	↓	–	Di Filippo et al. (2008)
	TMEV-IDD	Spinal cord	↑	–	Loría et al. (2008)
	RR-MS	T cells, B cells, NK cells	Increased in NK cells	–	Sánchez López et al. (2015)
DAGL/ MAGL	EAE	–	–	Inhibition of MAGL ameliorates EAE progression	Hernández-Torres et al. (2014)
CB_1	Lewis EAE rats	Brain	↓	Worsening of disease development and neurological impairment	Cabranes et al. (2005)
	P-MS	Plasma	↑	Disease progression	Jean-Gilles et al. (2009)
	MS plaques	Neurons, oligodendrocytes, infiltrated T cells	↑	Disease progression	Benito et al. (2007)
	RR-MS	T cells, B cells, NK cells	↑in T cells	–	Sánchez López et al. (2015)
CB_2	TMEV-IDD	Spinal cord	↑	–	Loría et al. (2008)
	P-MS	Plasma	↑	Disease progression	Jean-Gilles et al. (2009)
	MS plaques	Infiltrated T cells, astrocytes, microglia	↑	Disease progression	Benito et al. (2007)
	RR-MS	mDC and pDC	↑in mDC and ←→in pDC	Lack of immunoregulation	Chiurchiù et al. (2013)
	RR-MS	T cells, B cells, NK cells	Increased in B cells	–	Sánchez López et al. (2015)

CSF, cerebrospinal fluid; EAE, experimental autoimmune encephalomyelitis; mDC, myeloid dendritic cells; RR, relapsing-remitting; P, progressive; pDC, plasmacytoid dendritic cells; PP, primary progressive; SP, secondary progressive; TMEV-IDD, Theiler's murine encephalomyelitis virus-induced demyelinating disease. ↑, increase; ↓, decrease; ←→, unchanged.

สัตว์ทดลอง

คน

แบบและระยะต่างๆของโรค

กลไลที่เกิดขึ้นในระยะต่างๆ

เซลล์ในสมอง

เซลล์ในระบบภูมิคุ้มกัน

ระบบ **eCannabinoid**

overt disease state
alterations in endocannabinoid signaling

- From expression and function of cannabinoid receptors and endocannabinoid metabolic enzymes
- From modified endocannabinoid tissue concentrations
- Therapies: agonists or antagonists of CB1 or CB2 or from inhibitors of endocannabinoid degradation or biosynthesis.
- CB1 overactivation may contribute to the progression or symptoms of a disease — such as obesity, type 2 diabetes, hepatic or kidney disorders and even some neurological conditions such as Alzheimer disease and schizophrenia

PROBLEMS IN DESIGNING RX:
not that easy just to stimulate/block receptor

- **use of systemic direct or inverse agonists may indiscriminately activate or inhibit the function of all CB1 molecules, can interfere with normal CB1 function in non-target cells.**
- anxiety and depression caused by **CB1 antagonists** or **inverse agonists.**
- rimonabant (Acomplia), a CB1 inverse agonist marketed in Europe in 2006 for the treatment of obesity and the metabolic syndrome, had to be withdrawn in 2008 because it induced depression and suicidal ideation in a subset of patients.

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CB_1 KNOCK-OUT MICE

- CB1 cannabinoid receptor knockout in mice leads to leanness, resistance to diet-induced obesity and enhanced leptin sensitivity. CB_1 knock-out mice are healthy and live into adulthood [*Int. J. Obes. Relat. Metab. Disord.* 28 (4): 640–8].
- Compared to wildtype, CB_1 knock-out mice exhibit severe deficits in motor learning, memory retrieval, and increased difficulty in completing the Morris water maze.[5][53][54]
- There is also evidence indicating that these knockout animals have an increased incidence and severity of stroke and seizure.

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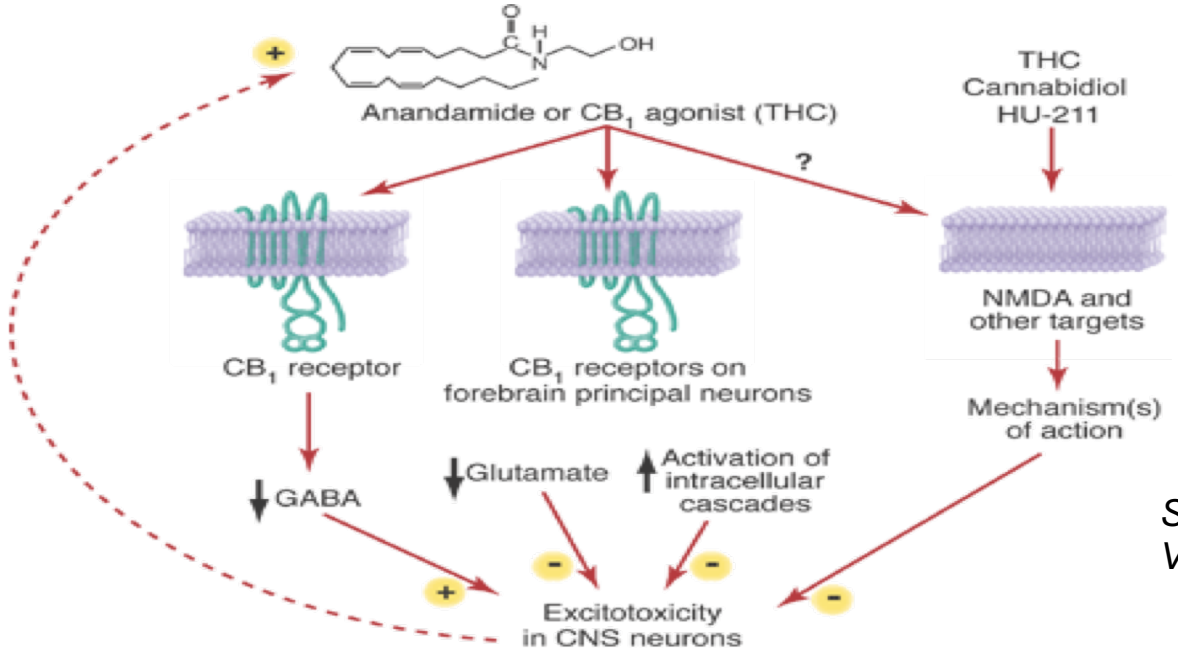
The CB receptor paradox



Science 3 October 2003:
Vol. 302 no. 5642 pp. 65-67

Stimulation of CB_1 receptors located on principal forebrain neurons provides protection against excitotoxicity by both dampening neuronal activity through blocking presynaptic release of glutamate and activating intracellular signaling cascades that might contribute to long-term adaptive cellular changes. The endocannabinoid anandamide is produced in the hippocampus in response to excessive neuronal excitability. Anandamide stimulates CB_1 receptors on principal neurons of the forebrain that protect against excitotoxic damage. Conversely, stimulation of CB_1 receptors on GABAergic interneurons of the cortex further augments excitotoxicity. Finally, THC, the psychoactive constituent of cannabis, as well as the nonpsychoactive compounds cannabidiol (natural) and HU-211 (Dexanabinol) exert their neuroprotective effects in part through a mechanism that does not involve CB_1 receptors.

Enzyme Inhibitors (e.g., AEA degradation)

Indirect enhancers of CB activity—more selective, less side effects
What have we learned?

FAAH inhibitors

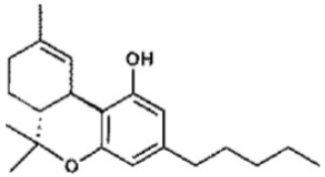
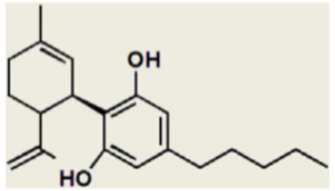
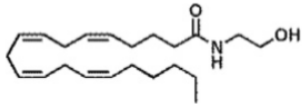
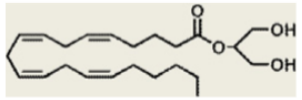
ECB

- Reduce anxiety-like behaviors
- Reduce depression-like behaviors
- Enhance social behavior in ASD models
- Reduce nicotine addiction
- May be effective for cannabis use disorder

Very mild side effect profile in animals and humans

Piomellli, 2016

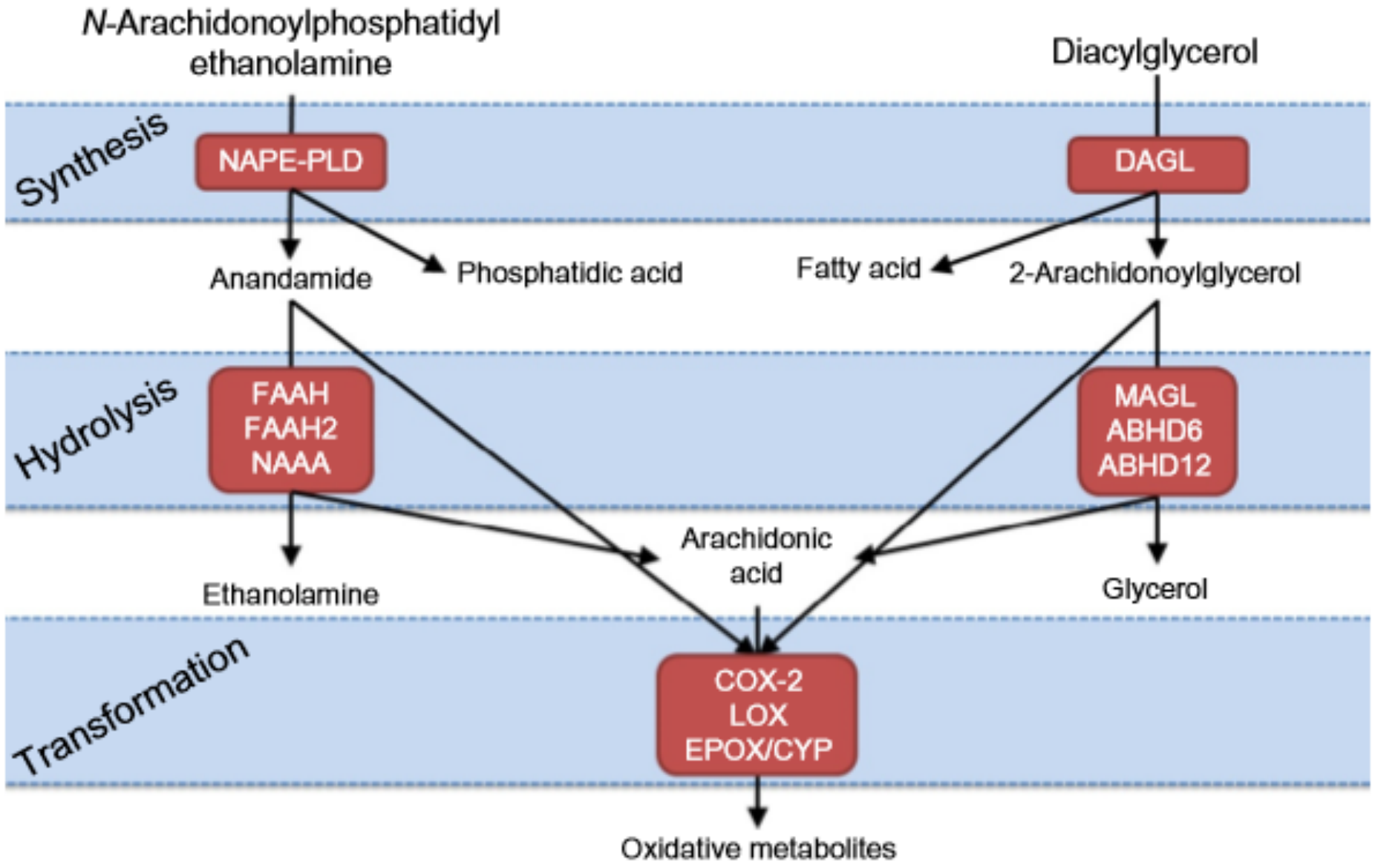
Major (endo)cannabinoids, and main metabolic enzymes of eCBs with a role in neuroinflammation.

Name (abbreviation)	Chemical structure
Δ^9-Tetrahydrocannabinol (THC)	
Cannabidiol (CBD)	
N-Arachidonoylethanolamine (Anandamide, AEA)	
2-Arachidonoylglycerol (2-AG)	
Biosynthetic enzyme of AEA	**Intracellular localization**
N-acylphosphatidyl ethanolamines (NAPE)-specific phospholipase D (NAPE-PLD)	Membrane-associated
Biosynthetic enzymes of 2-AG	**Intracellular localization**
Diacylglycerol lipase α (DAGLα)	Membrane-associated
Diacylglycerol lipase β (DAGLβ)	Membrane-associated
Degrading enzyme of AEA	**Intracellular localization**
Fatty acid amide hydrolase (FAAH)	Membrane-associated (mainly ER)
Degrading enzyme of 2-AG	**Intracellular localization**
Monoacylglycerol lipase (MAGL)	Membrane-associated and cytosolic

Progress in neurobiology 2018

ลดการทำงานของ **FAAH** เพิ่ม **AEA**

หรือเพิ่ม **AEA** จาก **CBD**



Fowler CJ et al. chapter 2. Advance in Pharmacology 2017

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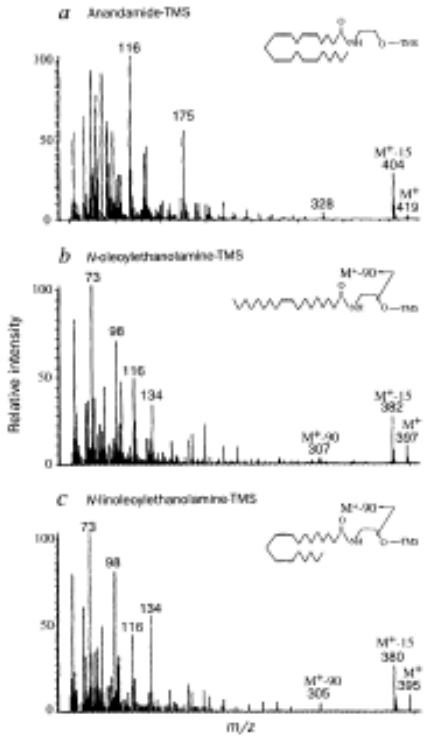
Brain cannabinoids in chocolate

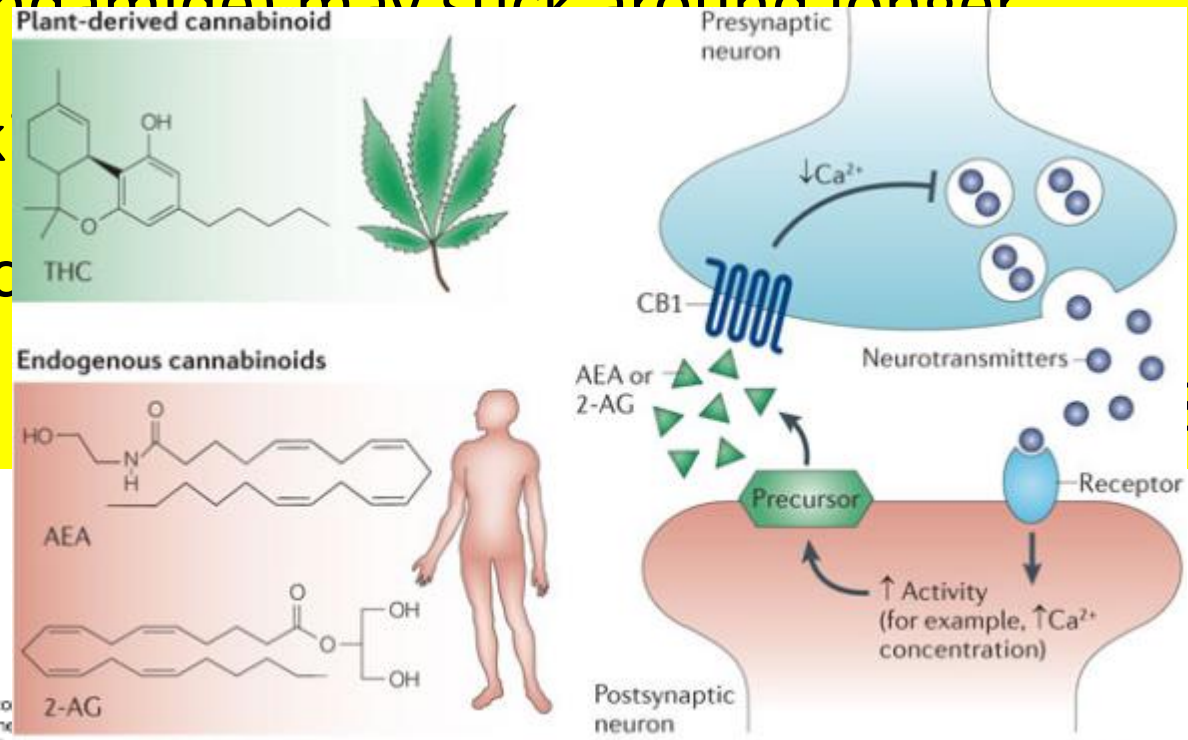
SIR — Chocolate craving, common in western societies, is still incompletely understood. Although sensory components of the nervous system are likely to be essential[1], the association of chocolate craving with certain drug-induced psychoses[2] suggests that pharmacologically active substances could also be involved. Attention in this respect has been focused primarily on the methylxanthines[3], which are thought to act as competitive antagonists at adenosine receptors[4]. We report here on a novel group of pharmacological constituents of chocolate, whose main target may be the endogenous cannabinoid system of the brain.

Anandamide (*N*-arachidonoylethanolamine) is a brain lipid that binds to cannabinoid receptors with high affinity and mimics the psychoactive effects of plant-derived cannabinoid drugs[5]. It is released from neurons[6] and is rapidly broken down by a selective enzyme activity[7], suggesting that it may be an endogenous cannabinoid neurotransmitter or neuromodulator. We considered that chocolate, which is rich in fat, might contain lipids chemically and pharmacologically

coylethanolamine inhibit anandamide hydrolysis in rat brain microsomes, a reaction catalysed by anandamide amidohydrolase activity[7] (Fig. 2*a*). Moreover, *N*-linoleoylethanolamine produces a similar inhibitory effect in intact cells. Rat cortical astrocytes in culture hydrolyse

- Chocolate may inhibit the natural breakdown of anadamide. This means that natural anandamide (or introduced anandamide) may stick around longer mak choc





Why other forms of THC and CBD may be needed?

Table 3 | **Proposed key molecular targets for the most studied non-psychotropic phytocannabinoids**

Phytocannabinoid	Effect on CB1 and CB2	Effect on TRP channels	Effect on PPARs and orphan GPCRs	Effect on enzymes and transporters	Effect on neurotransmitter receptors and voltage-dependent ion channels	Potential therapeutic uses	Refs
CBD	Negative allosteric modulator for CB1[a]	• TRPV1 (+) • TRPV2 (+) • TRPV3 (+)[a] • TRPA1 (+) • TRPM8 (–)	• PPARγ (+) • GPR55 (–) • GPR3 (–)[a] • GPR6 (–)[a] • GPR12 (–)[a]	• FAAH (–) • ENT (–) • eCB transport across the membrane (–)	• 5-HT_{1A} (+) • Glycine receptors (+) • $GABA_AR$ (+)[a] • Ca_V3s (–) • Ca_V1s (–) • $Na_v1.6$ (–)[a] • VDAC1 (–)[a]	Chronic and inflammatory pain, epilepsy, IBDs, schizophrenia, cancer and neuroinflammatory diseases	64,67,68,199, 202,255–260
CBDV	None	• TRPV1 (+) • TRPA1 (+) • TRPM8 (–)	None	• DGLα (–)[a] • eCB transport across the membrane (–)[a]	None	Epilepsy	67,68,199,256
CBDA	None	None	PPARγ (+)	• DGLα (–)[a] • NAAA (–)[a]	Positive allosteric modulator for 5-HT_{1A}[a]	Nausea and cancer	199,202,256, 261,262
THCV	• CB1 (–) • CB2 (+)	• TRPV1 (+) • TRPV2 (+) • TRPV3 (+) • TRPA1 (+)[a] • TRPM8 (–)	None	None	5-HT_{1A} (+)[a]	Obesity, metabolic syndrome, insulin resistance, steatosis, schizophrenia and inflammatory pain	67,199,256, 257,263
CBG	Weak CB2 agonist	• TRPV1 (+) • TRPV2 (+) • TRPA1 (+) • TRPM8 (–)	PPARγ (+)	eCB transport across the membrane (–)[a]	• ADRA2 (+)[a] • 5-HT_{1A} (–)[a]	Cancer, neurodegenerative diseases and IBDs	67,202,256, 257,261,264
CBC	None	TRPA1 (+)	None	• ENT (–)[a,b] • eCB transport across the membrane (–)[a]	None	Pain and gliosis	67,199, 256,260
THCA	None	None	PPARγ (+)	• DGLα (–)[a] • MAGL (–)[a]	None	Neurodegenerative diseases	67,256,261

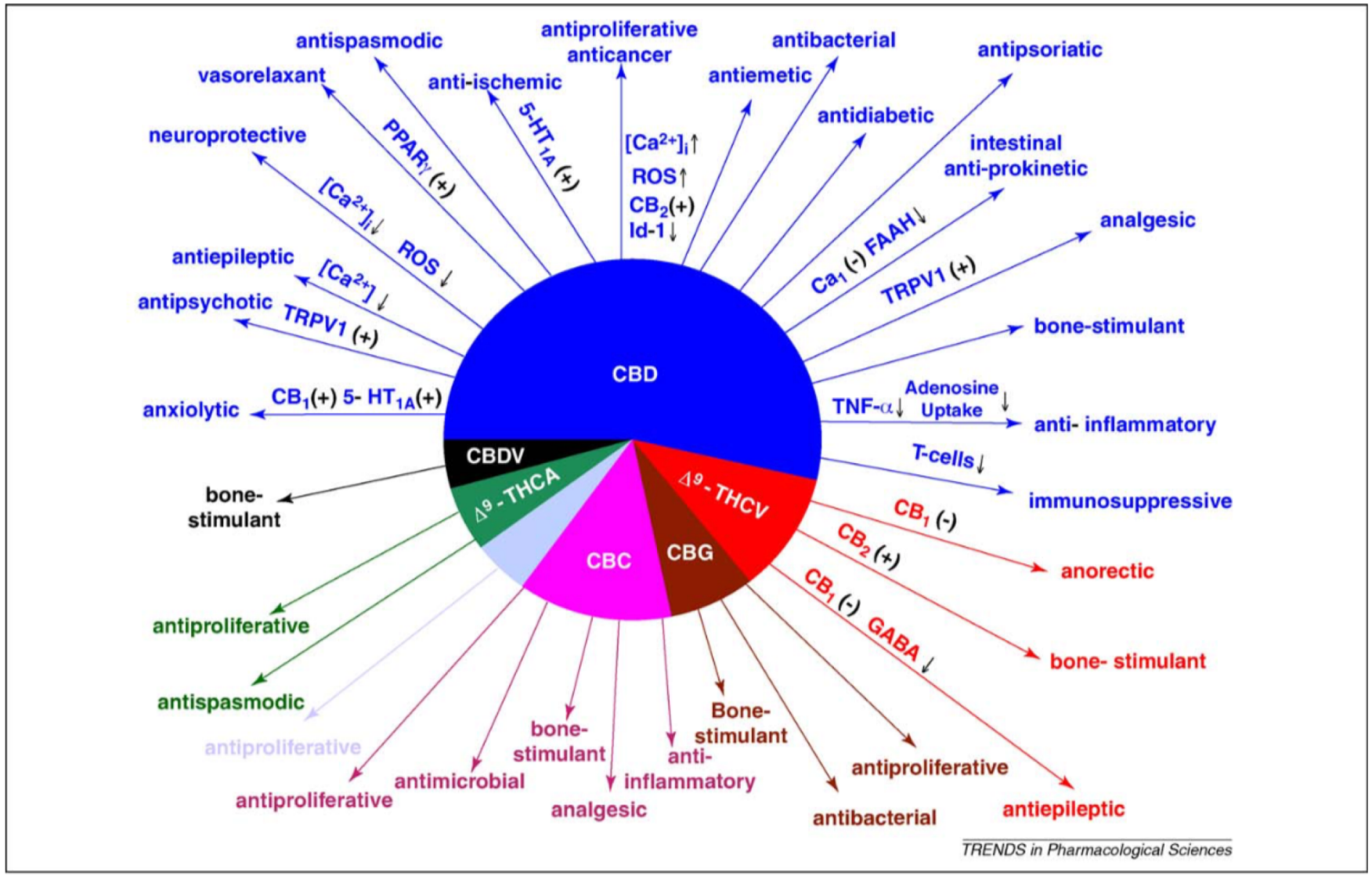
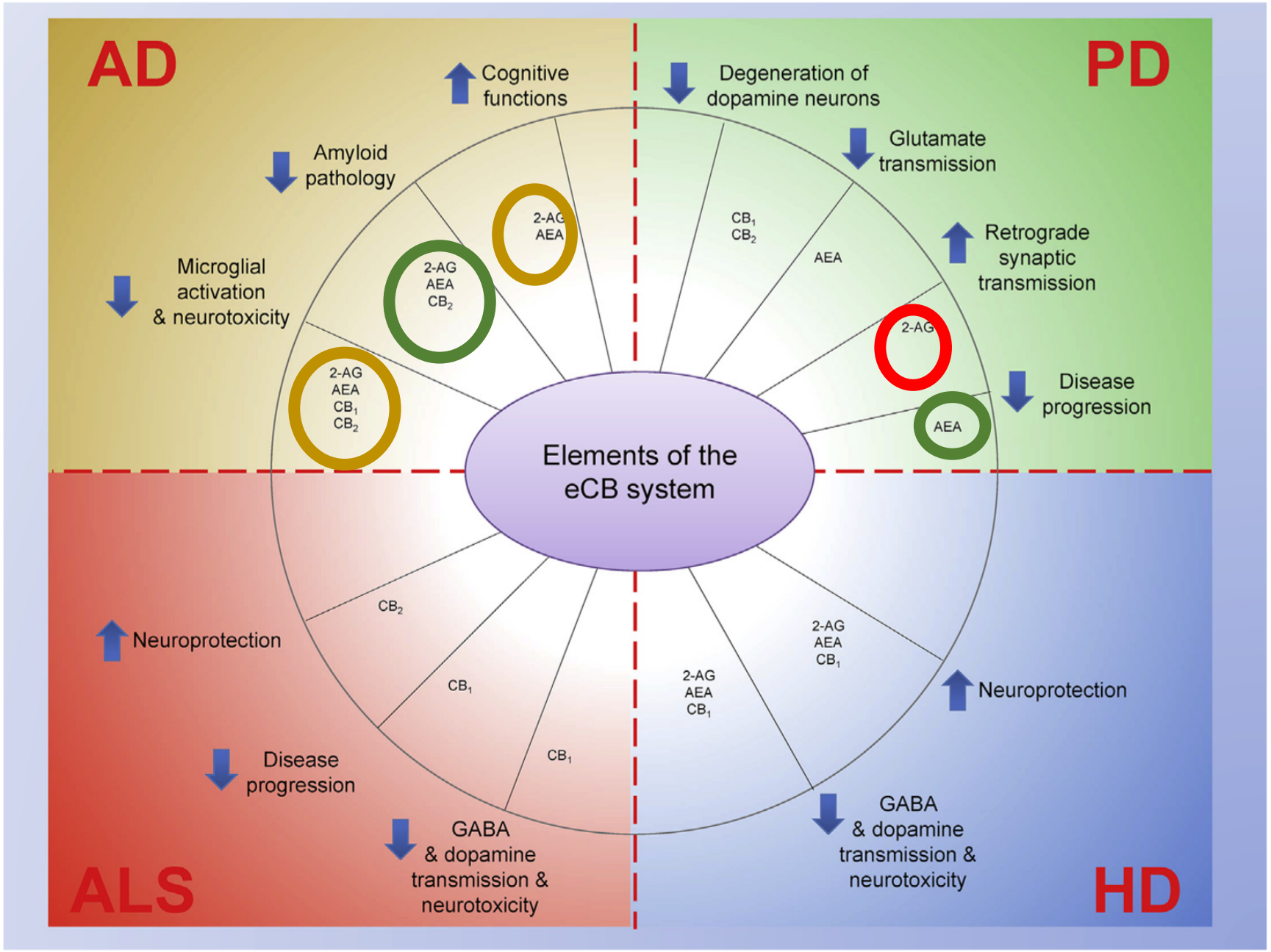


Figure 1. Pharmacological actions of non-psychotropic cannabinoids (with the indication of the proposed mechanisms of action).
Abbreviations: Δ^9-THC, Δ^9-tetrahydrocannabinol; Δ^8-THC, Δ^8-tetrahydrocannabinol; CBN, cannabinol; CBD, cannabidiol; Δ^9-THCV, Δ^9-tetrahydrocannabivarin; CBC, cannabichromene; CBG, cannabigerol; Δ^9-THCA, Δ^9-tetrahydrocannabinolic acid; CBDA, cannabidiolic acid; TRPV1, transient receptor potential vanilloid type 1; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; 5-HT_{1A}, 5-hydroxytryptamine receptor subtype 1A; FAAH, fatty acid amide hydrolase.
(+), direct or indirect activation; ↑, increase; ↓, decrease.

AEA
2 AG

THC et al
CBD et al
others



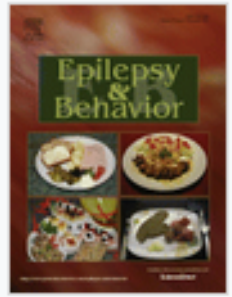
Lesson learnt

- What seems to be sounded may have paradoxical effect
- Responses may be different in type or dosage according to individual with similar diseases
- Particular attention on selection of patient and on appropriate choice of preparation, route according to comorbid status, concomitant drug usage, etc
- MEDICAL USE OF CANNABIES IS AN ART

Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy

Brenda E. Porter, and Catherine Jacobson

Epilepsy and Behavior, 2013-12-01, Volume 29, Issue 3, Pages 574-577



Abstract

Severe childhood epilepsies are characterized by frequent seizures, neurodevelopmental delays, and impaired quality of life. In these treatment-resistant epilepsies, families often seek alternative treatments. This survey explored the use of cannabidiol-enriched cannabis in children with treatment-resistant epilepsy. The survey was presented to parents belonging to a Facebook group dedicated to sharing information about the use of cannabidiol-enriched cannabis to treat their child's seizures. Nineteen responses met the following inclusion criteria for the study: a diagnosis of epilepsy and current use of cannabidiol-enriched cannabis. Thirteen children had Dravet syndrome, four had Doose syndrome, and one each had Lennox–Gastaut syndrome and idiopathic epilepsy. The average number of antiepileptic drugs (AEDs) tried before using cannabidiol-enriched cannabis was 12. Sixteen (84%) of the 19 parents reported a reduction in their child's seizure frequency while taking cannabidiol-enriched cannabis. Of these, two (11%) reported complete seizure freedom, eight (42%) reported a greater than 80% reduction in seizure frequency, and six (32%) reported a 25–60% seizure reduction. Other beneficial effects included increased alertness, better mood, and improved sleep. Side effects included drowsiness and fatigue. Our survey shows that parents are using cannabidiol-enriched cannabis as a treatment for their children with treatment-resistant epilepsy. Because of the increasing number of states that allow access to medical cannabis, its use will likely be a growing concern for the epilepsy community. Safety and tolerability data for cannabidiol-enriched cannabis use among children are not available. Objective measurements of a standardized preparation of pure cannabidiol are needed to determine whether it is safe, well tolerated, and efficacious at controlling seizures in this pediatric population with difficult-to-treat seizures.

MEDICAL MARIJUANA
&
EPILEPSY TREATMENT

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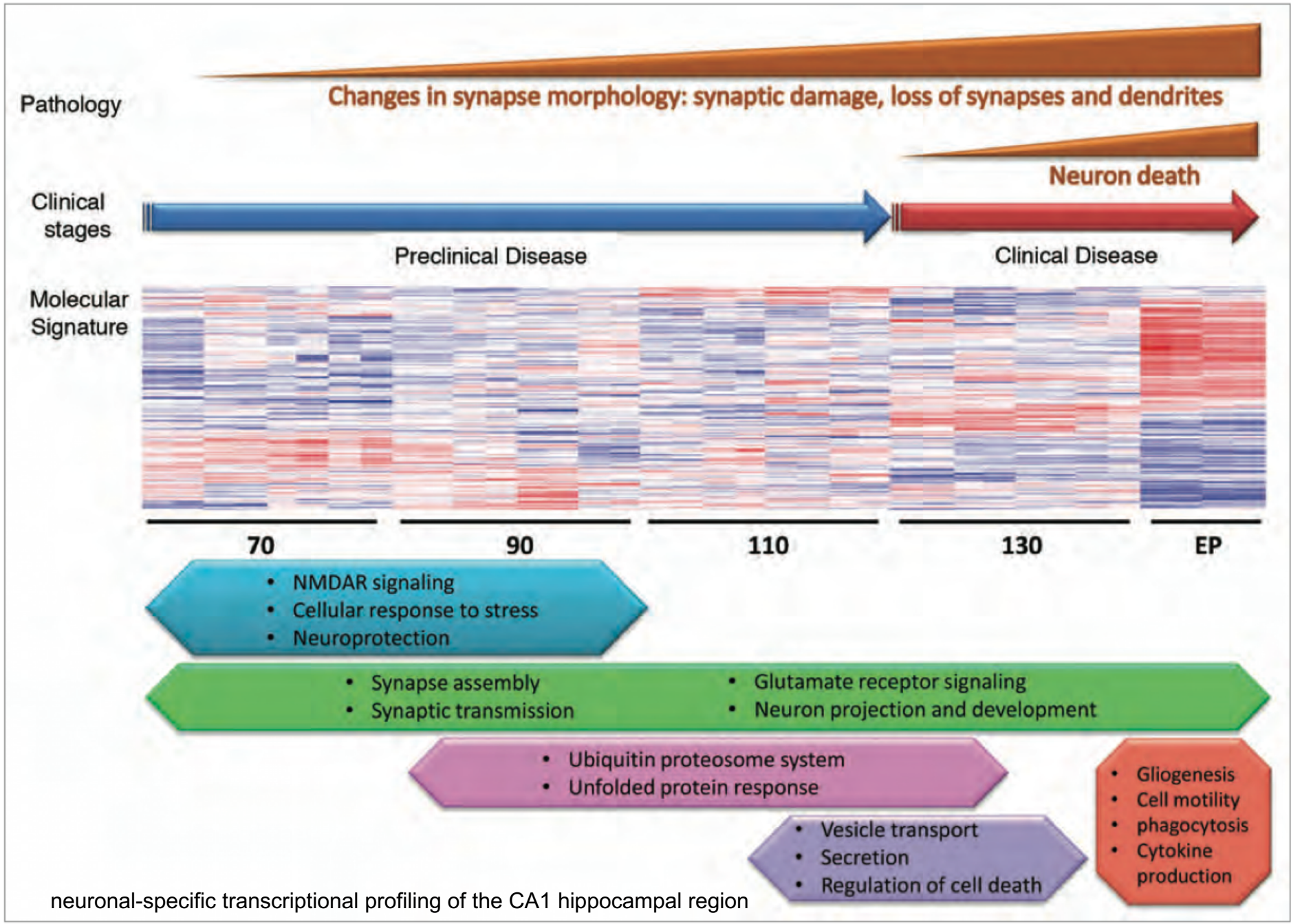
Table 1
Summary of survey responses.

Patient	Diagnosis	Age and sex	Age at seizure onset	Time on CBD	CBD (mg/kg/day)	THC (mg/kg/day)	Seizures before CBD	Seizures after CBD	Estimated change in seizure frequency	Number of AEDs tried before CBD	AEDs discontinued while on CBD
1	LGS	7 y, female	<1 y	>1 y	?	?	>100/day	8–10/day	>−80%	8	Banzel, Onfi
2	DS	14 y, female	<1 y	>4 m	14	0.5	5/day	0–1/day	>−80%	12	
3	EFMR	12 y, female	<1 y	2–4 m	7	0.5	12/day	0–1/day	>−80%	17	
4	DS	7 y, male	<1 y	>4 m	8	0.25−0.5	50/week	50/week	0	16	
5	DS	6 y, female	<1 y	>4 m	4	0.1–0.25	200–300/week	0–2/week	>−80%	6	Onfi
6	DS	16 y, female	<1 y	>4 m	1–2	0.02–0.1	7/week	4/week	−25%	16	Onfi
7	DS	13 y, male	<1 y	3–4 m	4	0.02–0.1	40/week	30/week	−25%	16	Phenobarbital, Depakote
8	DS		<1 y	>4 m	?	?	3/week	1–2/week	−50%	14	Klonopin
9	DS	Male	<1 y	>4 m	3–4	0.04–0.2	100–500/week	1–2/week	>−80%	10	STP, Topamax, Depakote
10	DS		<1 y	>4 m	4	0.2–0.4	200–300/week	20–50/week	>−80%	12	STP
11	DS	8 y, female	<1 y	>1 y	?	?	5–10/week	0–3/week	−60%	10	STP, Onfi, Depakote
12	DS	7 y, female	<1 y	>4 m	3–4	0.04–0.2	20+/week	0–10/week	−50%	10	Onfi, Zonegran, Depakote
13	Doose	9 y, female	<1 y	>4 m	10–13	0.5	60–250/day	0	>−80%	15	Lorazepam, ethosuximide
14	DS	2 y, male	<1 y	>4 m	7	0.08–0.4	2/week	0	>−80%	4	
15	Doose		2–5 y	2 w	<0.5	0.01–0.05	1–7/week	1–7/week	0	13	
16	Doose	11 y, male	2–5 y	1–2 m	6	0.6–0.8	20/week	4/week	>−80%	13	
17	Doose		2–5 y	1–2 m	6	0	15–20/day	0–3/day	>−80%	14	Steroids
18	Idiopathic	Female	1–2 y	<1 m	28	0.5–0.7	10/week	8/week	−25%	5	Valproic acid
19	DS	6 y, female	<1 y	>4 m	1	0.06–0.3	3/week	3/week	0	?	

LGS, Lennox–Gastaut syndrome; DS, Dravet syndrome; EFMR, epilepsy in females with mental retardation; STP, stiripentol; y, year/years; m, month/months; w, weeks.

CASCADES FROM DYSREGULATION IN SIGNALLING/ CELLULAR RESPONSE AND REPAIR/ER endoplasmic reticulum STRESS/ MITOCHONDRIAL DYNAMICS/ MICROCELLULAR-MACROCELLULAR DAMAGE

CLINICAL DISEASE



neuronal-specific transcriptional profiling of the CA1 hippocampal region

Table 1. Clinical and Immunologic Features and Antibody Effects of Antibody-Mediated Encephalitis.*

Antibody (No. of Patients)†	Median Age (Range); Male:Female Ratio	Main Clinical Features on Presentation	Main Syndrome	Findings on MRI (% of Patients)‡	Frequency of Cancer (% of Patients)	Predominant IgG Class	In Vitro Antibody Effects
NMDAR (>1500)	21 yr (2 mo–85 yr); 1:4	Children: seizures, dyskinesias; adults: behavioral changes, psychiatric symptoms	NMDAR encephalitis	Normal findings (70) or nonspecific changes	Varies with age and sex; ovarian teratoma in women 18–45 yr old (58)§	IgG1	Internalization of NMDAR, disruption of NMDAR interaction with ephrin-B2 receptor
AMPAR (80)	56 yr (23–81); 1:2.3	Confusion, memory loss; in rare cases, psychiatric symptoms	Limbic encephalitis	Increased signal in medial temporal lobes (67)	SCLC, thymoma, or breast cancer (56)	IgG1	Internalization of AMPARs
$GABA_BR$ (80)	61 yr (16–77); 1.5:1	Seizures, memory loss, confusion	Limbic encephalitis, prominent seizures	Increased signal in medial temporal lobes (45)	SCLC (50)	IgG1	Blocking of agonist effect of baclofen on $GABA_BR$
LGI1 (400)	64 yr (31–84); 2:1	Memory loss, faciobrachial dystonic seizures, hyponatremia	Limbic encephalitis	Increased signal in medial temporal lobes (83)	Thymoma (<5)	IgG4	Inhibition of LGI1 interaction with ADAM22 and ADAM23; decrease in postsynaptic AMPAR
CASPR2 (120)	66 yr (25–77); 9:1	Memory loss, insomnia, dysautonomia, ataxia, peripheral-nerve hyperexcitability, neuropathic pain	Limbic encephalitis¶‖	Increased signal in medial temporal lobes (67)	Varies with the syndrome (<5 overall)**	IgG4	Alteration of gephyrin clusters in inhibitory synapses
mGluR5 (11)	29 yr (6–75); 1.5:1	Confusion, psychiatric symptoms	Encephalitis	Normal findings in 5 of 11 patients	Hodgkin's lymphoma in 6 of 11 patients	IgG1	Decrease in density of surface mGluR5
D2R (25)	6 yr (2–15); 1:1	Parkinsonism, dystonia, psychiatric symptoms	Basal ganglia encephalitis	Increased signal in basal ganglia (50)	No associated cancer	Unknown	Receptor internalization and decrease in D2R surface density
DPPX (45)	52 yr (13–76); 2.3:1	Confusion, diarrhea, weight loss	Encephalitis, myoclonus, tremors, hyperekplexia¶	Normal findings or nonspecific changes (100)	B-cell neoplasms (<10)	IgG4	Decrease in density of surface DPPX and Kv4.2
$GABA_AR$ (70)	40 yr (2 mo–88 yr); 1:1	Seizures, confusion, behavioral changes	Encephalitis, frequent status epilepticus	Cortical and subcortical FLAIR signal abnormalities involving two or more brain regions (77)	Thymoma (27)	IgG1	Selective reduction of $GABA_AR$ at synapses
Neurexin-3α (6)	44 yr (23–57); 2:4	Confusion, seizures	Encephalitis	Normal findings in 4 of 6 patients	No associated cancer	Unknown	Decrease in density of surface neurexin-3α and total number of synapses in neurons undergoing development

* Data are from a review of studies.[1] ADAM denotes a disintegrin and metalloproteinase; AMPAR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2 contactin-associated protein–like 2; D2R dopamine 2 receptor; DPPX dipeptidyl-peptidase–like protein 6; GABA γ-aminobutyric acid; $GABA_AR$ GABA type A receptor; $GABA_BR$ GABA type B receptor; LGI1 leucine-rich, glioma-inactivated 1; mGluR5 metabotropic glutamate receptor 5; NMDAR *N*-methyl-D-aspartate receptor; and SCLC small-cell lung cancer.

† The number of patients is the approximate number reported.

‡ Data on brain abnormalities are based on T_2-weighted MRI of the head with fluid-attenuated inversion recovery (FLAIR). Unless otherwise indicated, MRI showed normal features or nonspecific changes.

§ The association with teratoma is sex- and age-dependent. Young women frequently have an ovarian teratoma, but the presence of a tumor is uncommon in children and young men.

¶ Most patients have progressive symptoms over a period of more than 3 months.

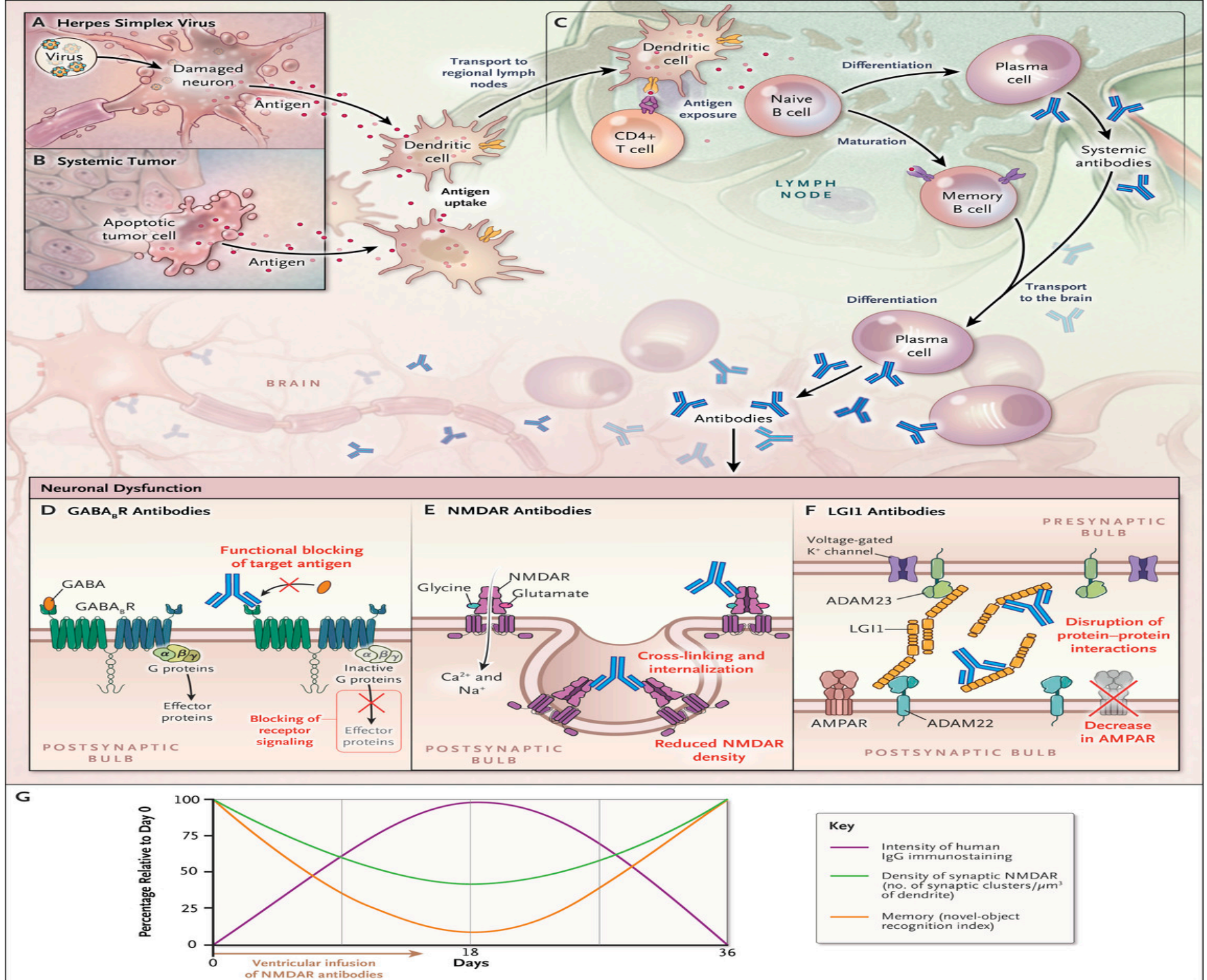
‖ CASPR2 antibodies are frequently associated with Morvan's syndrome, a chronic disorder characterized by neuromyotonia, cognitive deterioration, sleep dysfunction (agrypnia excitata), and autonomic features.

** The frequency of an underlying tumor in patients with CASPR2 antibodies varies according to the syndrome; although patients with limbic encephalitis rarely have an underlying tumor (but if they do, the type of tumor may vary from patient to patient), 40% of patients with Morvan's syndrome have an underlying thymoma.

J Dalmau, F Graus. N Engl J Med 2018;378:840-851.

ERROR IN SYNAPTIC AND INTRACELLLAR SIGNALLING

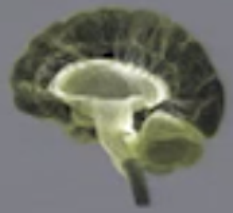
AUTOIMMUNE ENCEPHALITIS


A Herpes Simplex Virus
Virus
Damaged neuron
Antigen
B Systemic Tumor
Apoptotic tumor cell
Antigen
Transport to regional lymph nodes
Dendritic cell
Antigen uptake
C
Dendritic cell
Antigen exposure
CD4+ T cell
Naive B cell
Differentiation
Plasma cell
Maturation
Memory B cell
LYMPH NODE
Systemic antibodies
Transport to the brain
Differentiation
Plasma cell
BRAIN
Antibodies
Neuronal Dysfunction
D GABA$_B$R Antibodies
Functional blocking of target antigen
GABA
GABA$_B$R
G proteins
Effector proteins
Inactive G proteins
Blocking of receptor signaling
Effector proteins
POSTSYNAPTIC BULB
E NMDAR Antibodies
Glycine
NMDAR
Glutamate
Ca^{2+} and Na$^+$
Cross-linking and internalization
Reduced NMDAR density
POSTSYNAPTIC BULB
F LGI1 Antibodies
PRESYNAPTIC BULB
Voltage-gated K$^+$ channel
ADAM23
LGI1
Disruption of protein–protein interactions
AMPAR
ADAM22
Decrease in AMPAR
POSTSYNAPTIC BULB
G
Percentage Relative to Day 0
100
75
50
25
0
0
18
36
Days
Ventricular infusion of NMDAR antibodies
Key
Intensity of human IgG immunostaining
Density of synaptic NMDAR (no. of synaptic clusters/μm^3 of dendrite)
Memory (novel-object recognition index)

State of Science:
What we know…
Where we need more research…

The Developing Brain

Prevalence



- 45% of U.S. 12th graders have tried it
  - 21% used in past month
  - 6% use daily

Monitoring the Future, 2015

The Brain Continues to Mature into Early Adulthood.

Does Marijuana (and other substances) affect the developing brain and an individual's trajectory into adulthood?

Recovery of Cognition and CBF with Abstinence

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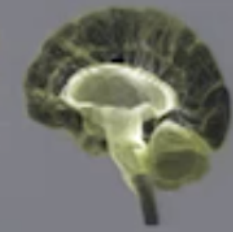
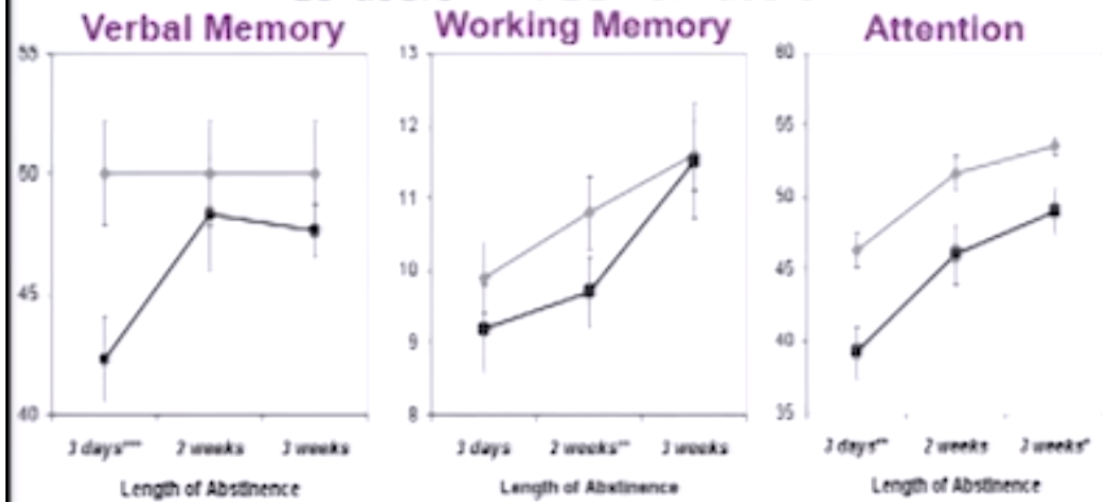
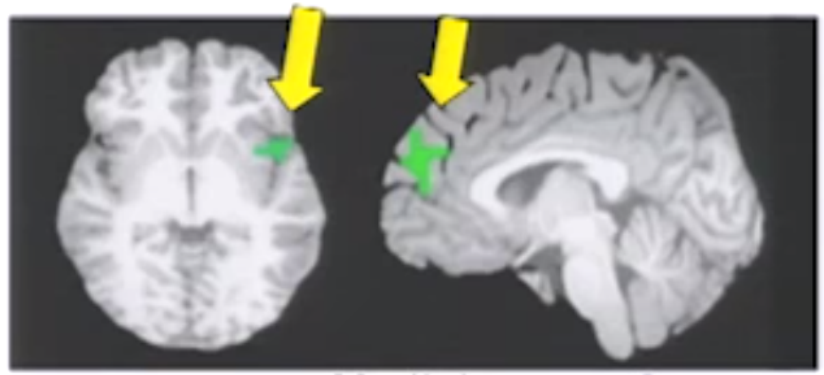
March 22-23, 2016



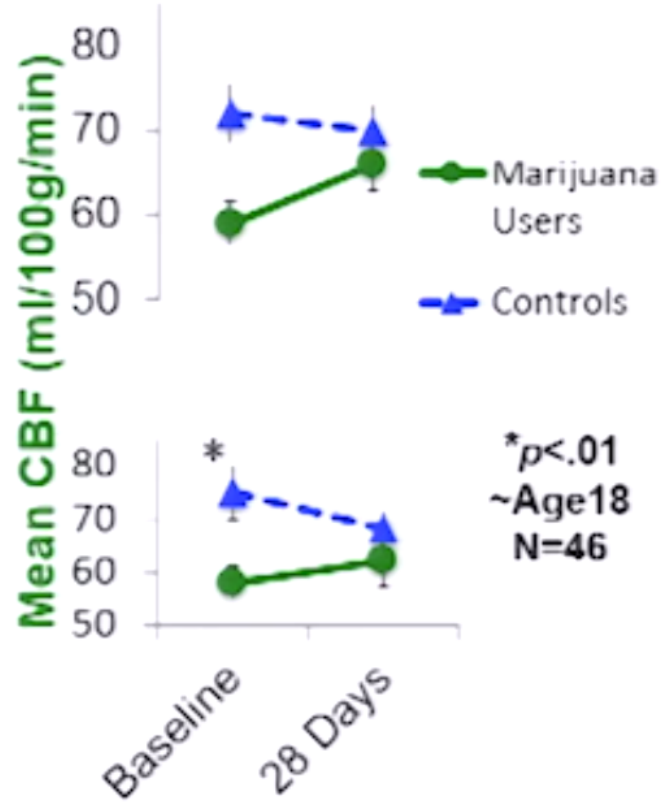
■19 users ◆21 non-users





Left Insula Medial Frontal Gyrus

Brain blood flow after 28 days monitored abstinence



*p<.01
~Age18
N=46

Tapert, 2016

Dunedin Study: IQ Declines in Subjects with Cannabis Dependence

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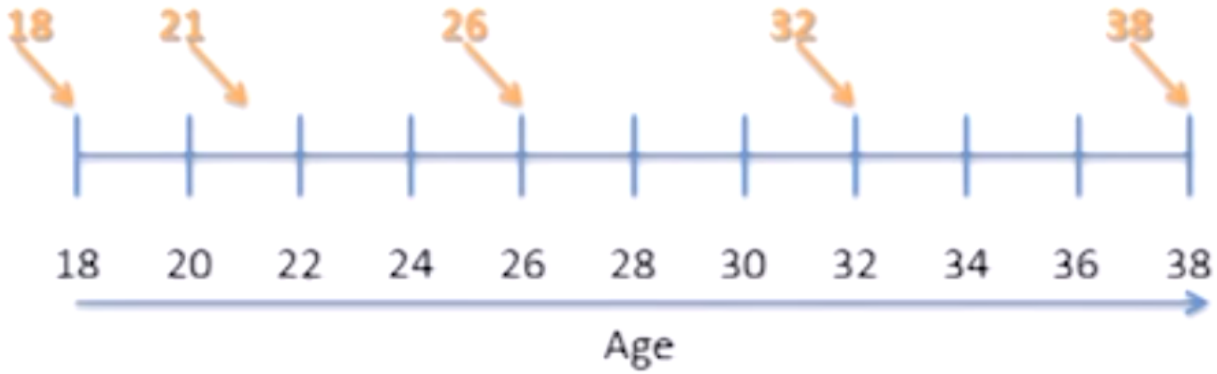

Persistence of Cannabis Dependence	N (%)	% Male
Never Used, Never Diagnosed	242 (28)	38.84
Used, Never Diagnosed	479 (55)	49.48
1 Diagnosis	80 (9)	70.00
2 Diagnoses	35 (4)	62.86
3+ Diagnoses	38 (4)	81.58

Meier, 2016

IQ Decline

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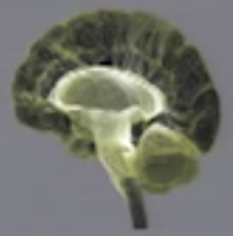


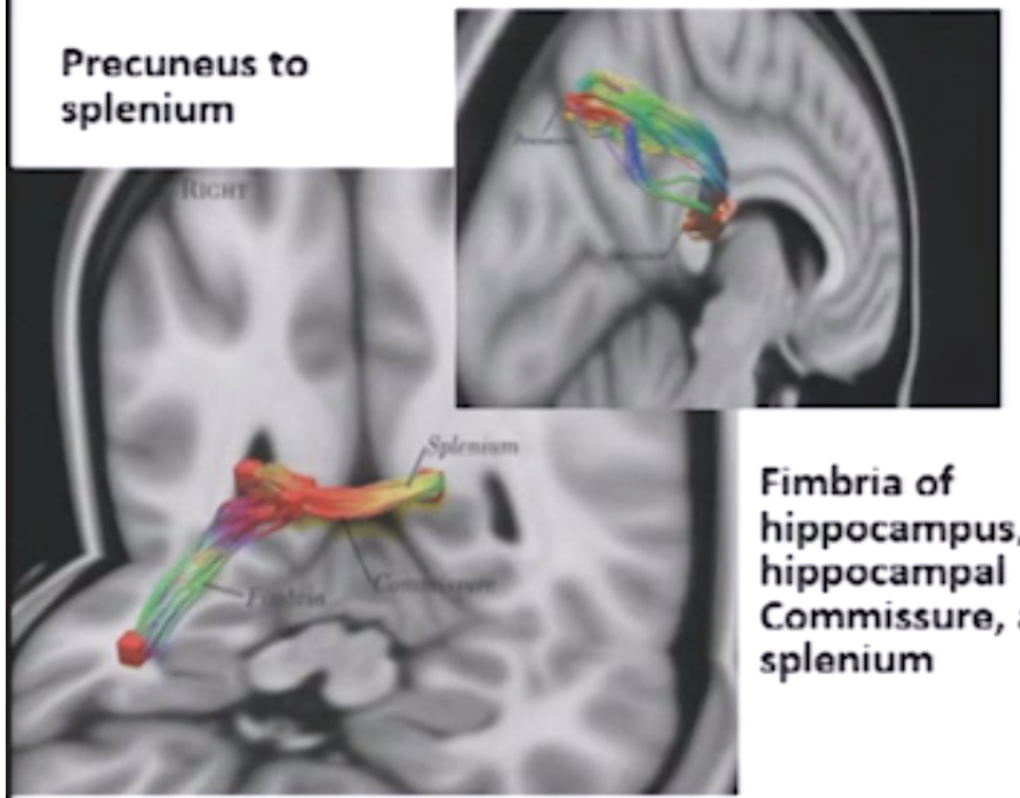
IQ Before and After Cannabis Use

Persistence of Cannabis Dependence	N	Age 7-13 Full-Scale IQ	Age 38 Full-Scale IQ	Δ in IQ
Never Used	242	99.84	100.64	+.80
Used, Never Diagnosed	479	102.32	101.25	-1.07
1 Diagnosis	80	96.40	94.78	-1.62
2 Diagnoses	35	102.14	99.67	-2.47
3+ Diagnoses	38	99.68	93.93	-5.75

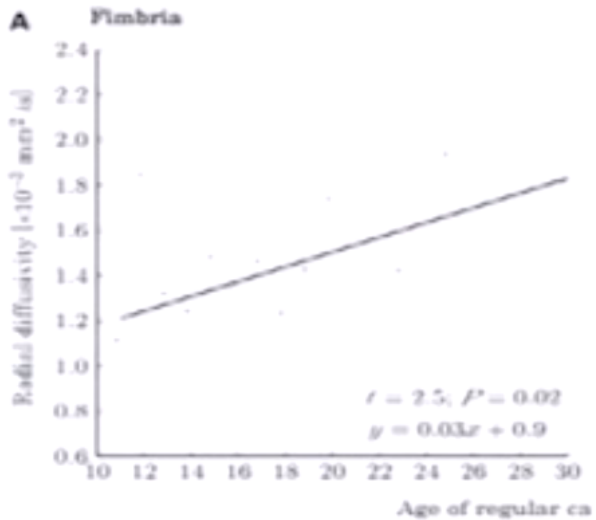
Meier, 2016

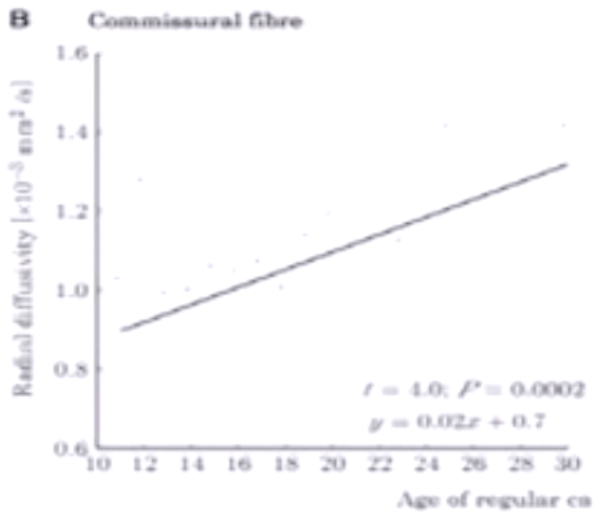
Brain Structure: Early (<18y) Long-Term Cannabis Use Decreases Axonal Fiber Connectivity

Precuneus to splenium



Fimbria of hippocampus, hippocampal Commissure, and splenium

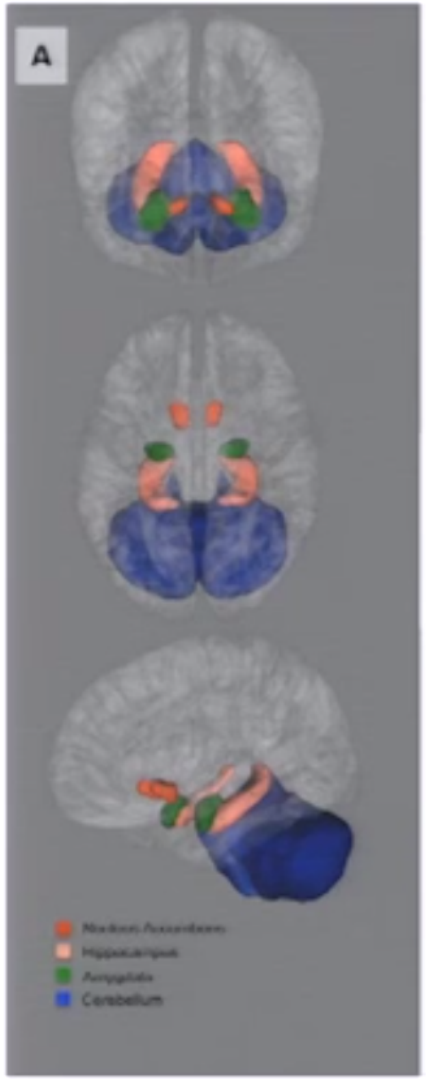




Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33).

Zalesky et al Brain 2012.

Subcortical Structures: No Differences Between Regular Marijuana Users and Nonusers



Welland B J et al. J. Neurosci. 2015;35:1505-1512

Adolescents – White Matter

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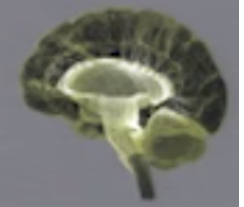
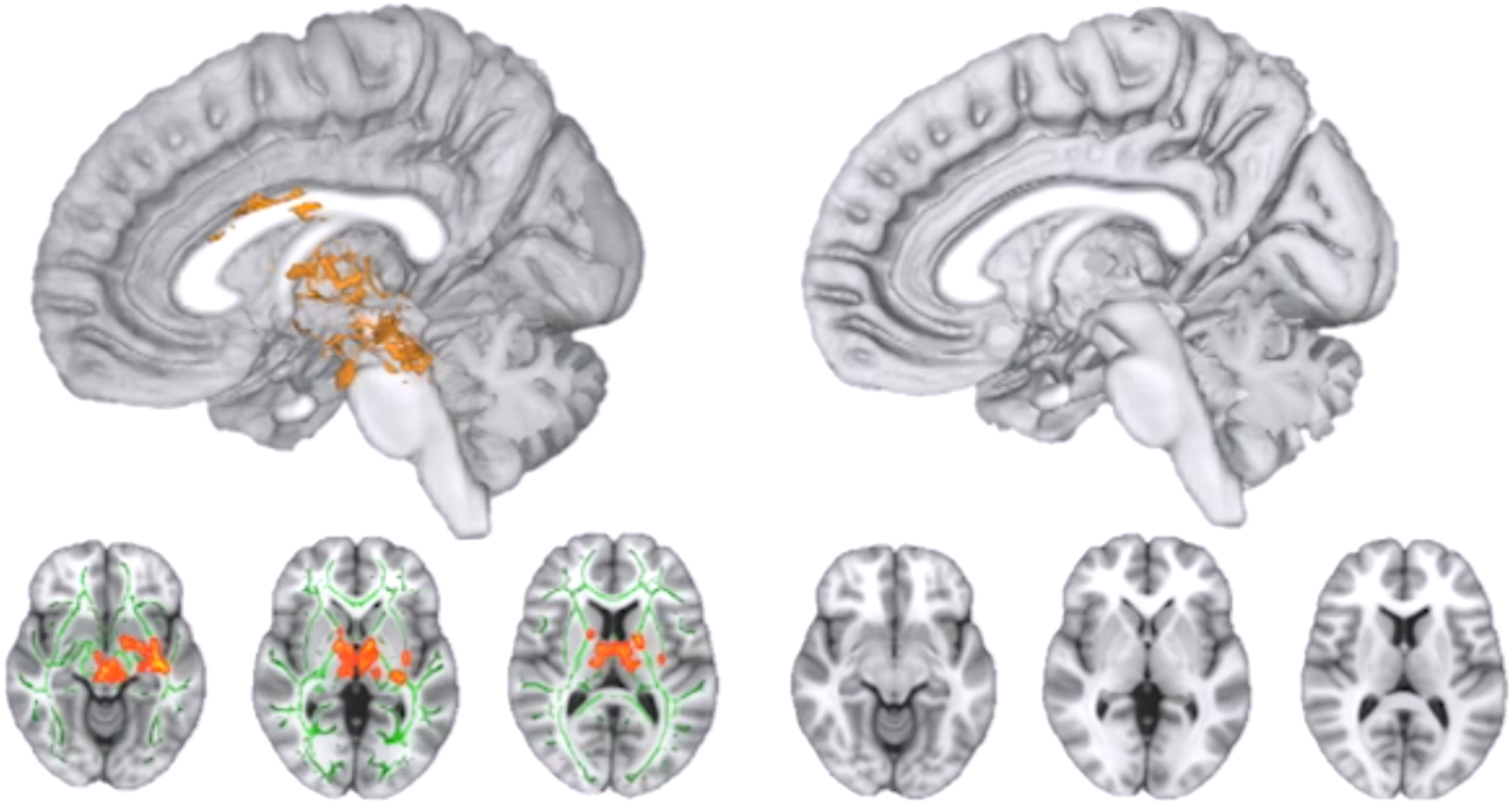


Alcohol Effects

Marijuana Effects



Hutchison, 2016

Adolescents & Marijuana

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What We Know:

- Adversely influences learning
- Effects on memory and attention outlast intoxication
- Appear worse with earlier age of onset, more chronic use
- Some neuroimaging data support these effects

What We Need to Know:

- Does cognitive ability (and corresponding brain alterations) recover with abstinence?
- What are the parameters of cannabis use sufficient to produce cognitive impairment?
- How does other drug use (e.g., alcohol, nicotine) influence outcomes?
- Are there individual/gender/other differences in susceptibility?
- How might dose/strain/potency differences affect cognitive impairment?

Need large longitudinal study to disentangle multiple interacting factors and examine individual differences.

Meier, Tapert, Hutchison, 2016

Adolescent Brain Cognitive Development (ABCD) National Longitudinal Study

NIDA, NIAAA, NCI, NICHD, NIMH, NIMHD, NINDS, OBSSR

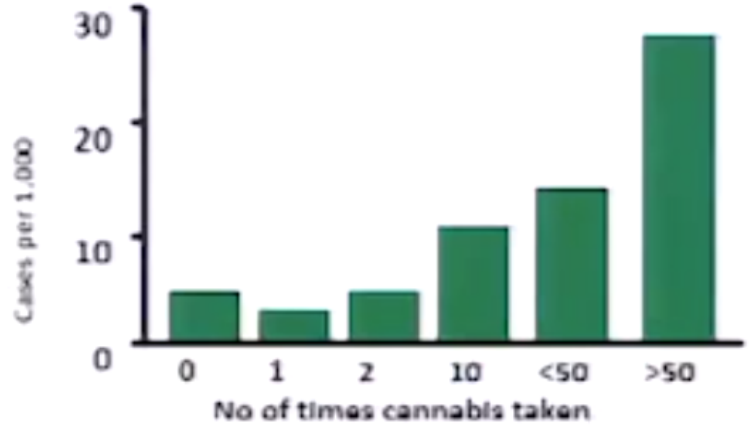
Ten year longitudinal study of 10,000 children from age 10 to 20 years to assess effects of childhood experiences, including use of *cannabis* and other substances on individual brain development trajectories

Adolescent Brain Cognitive Development

Teen Brains. Today's Science. Brighter Future.

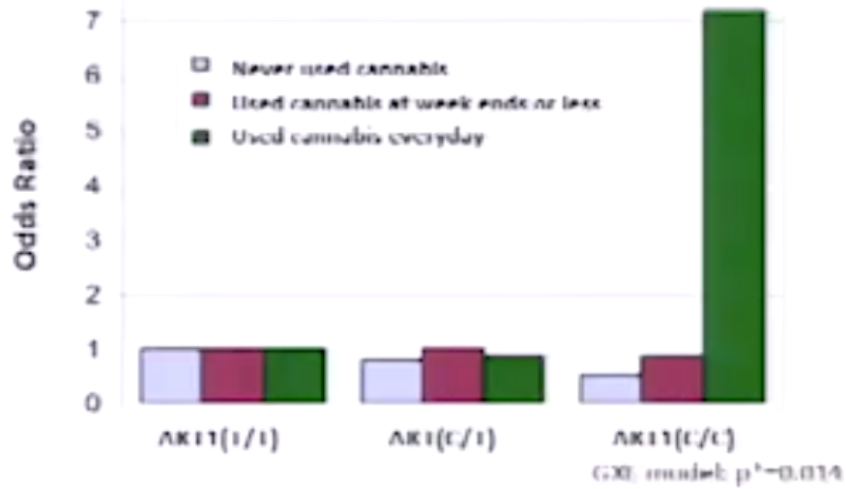
Cannabis-Associated Psychosis

Study of Swedish Conscripts (n=45570)



Andréasson et al Lancet, 1987.

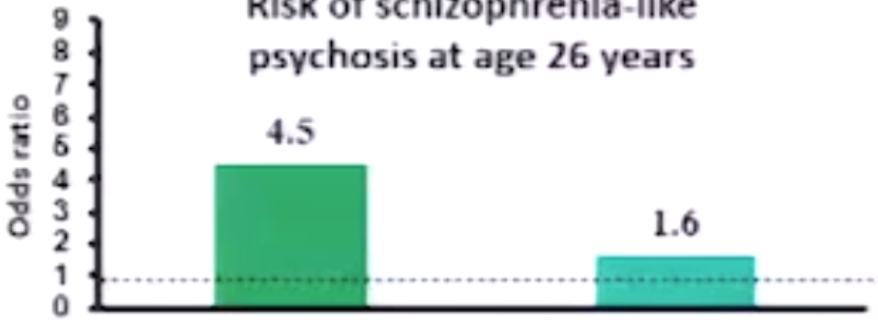
Regular Cannabis Use Increases Schizophrenia Risk in those with AKT1 rs2494732 genotype



Di Forti et al., Biological Psychiatry, 2012.

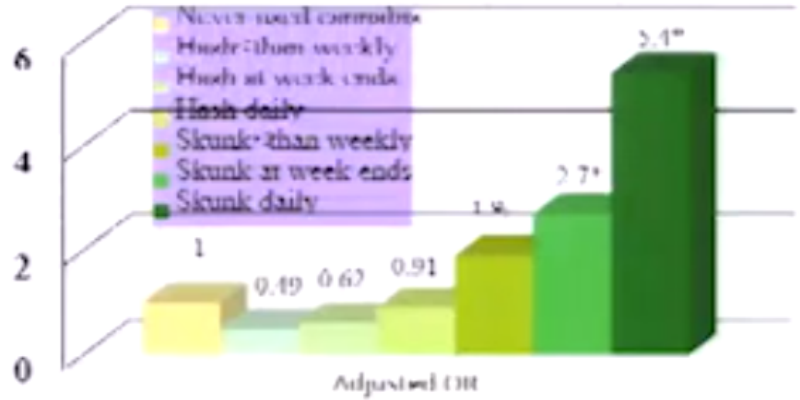
Prospective Dunedin study (n=1037)

Risk of schizophrenia-like psychosis at age 26 years



Arseneault et al BMJ 2002

Effect of High Potency Cannabis on Risk of Psychosis



Di Forti M et al., The Lancet published online February 18, 2015.

What We Need to Know:

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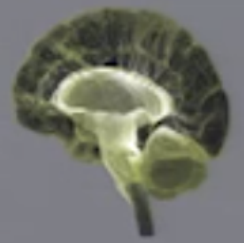
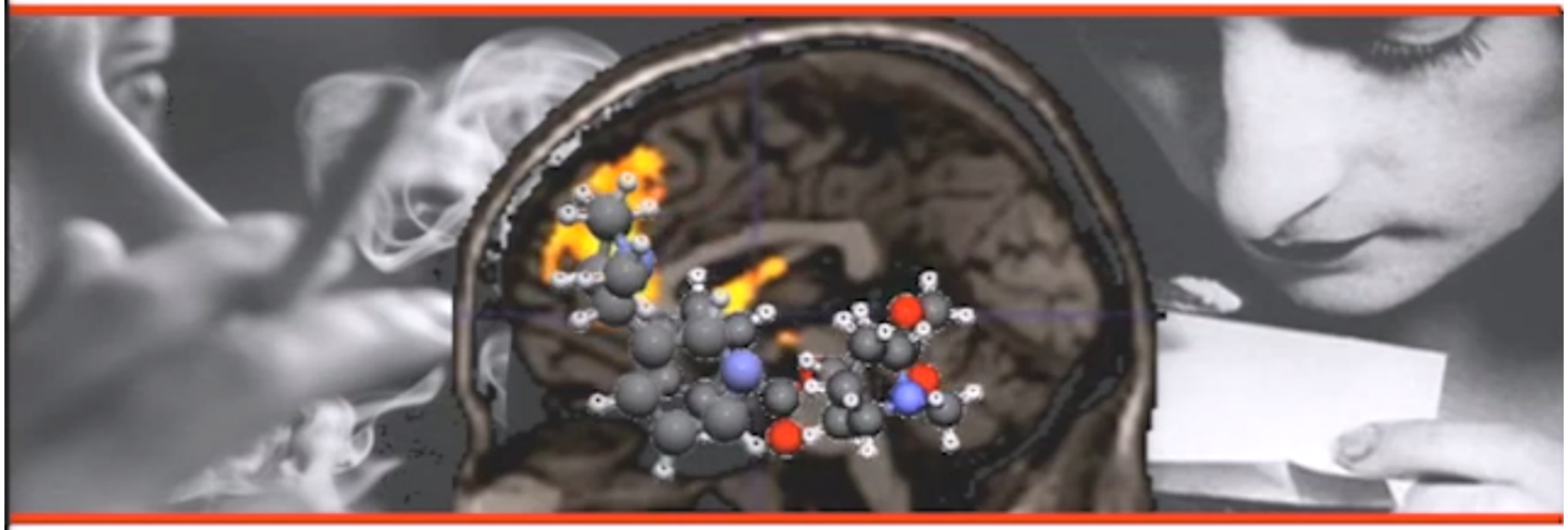


The precise nature of the association between cannabis use and the development of schizophrenia, including who is at risk.

- Discover factors that moderate the impact of cannabinoid exposure on risk for psychosis. Need longitudinal studies including high potency/synthetic.
- Clarify effect of cannabinoids on neurodevelopmental processes and brain structures relevant to psychotic disorders.
- In those at risk, are there identifiable protective factors that moderate the effect of cannabis exposure on psychosis / schizophrenia?
- Is there a physiologic basis for the observation that many with schizophrenia regularly use cannabis?

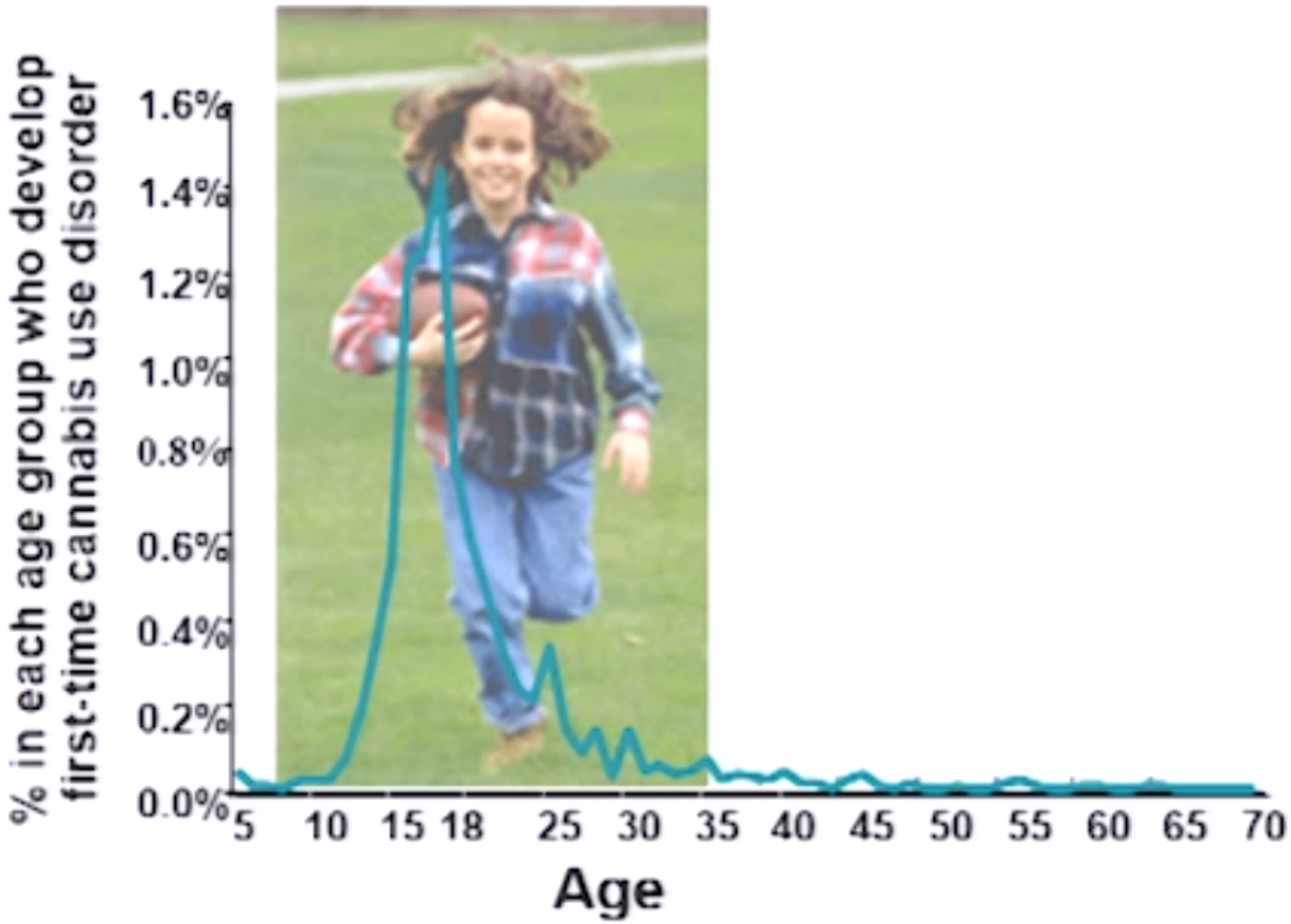
Evins, 2016

Disease of ADDICTION:
Significance to Brain Development, Function & Behavior



Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse
@NIDAnews

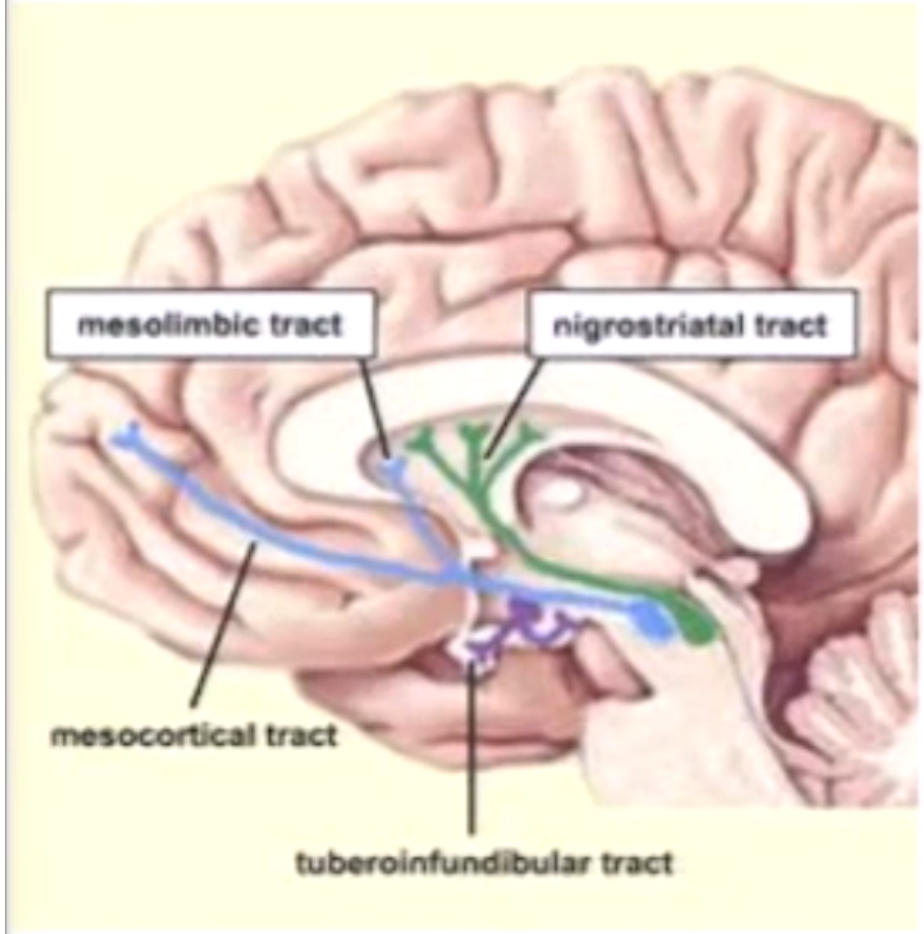
ADDICTION IS A DEVELOPMENTAL DISEASE
starts in adolescence and childhood

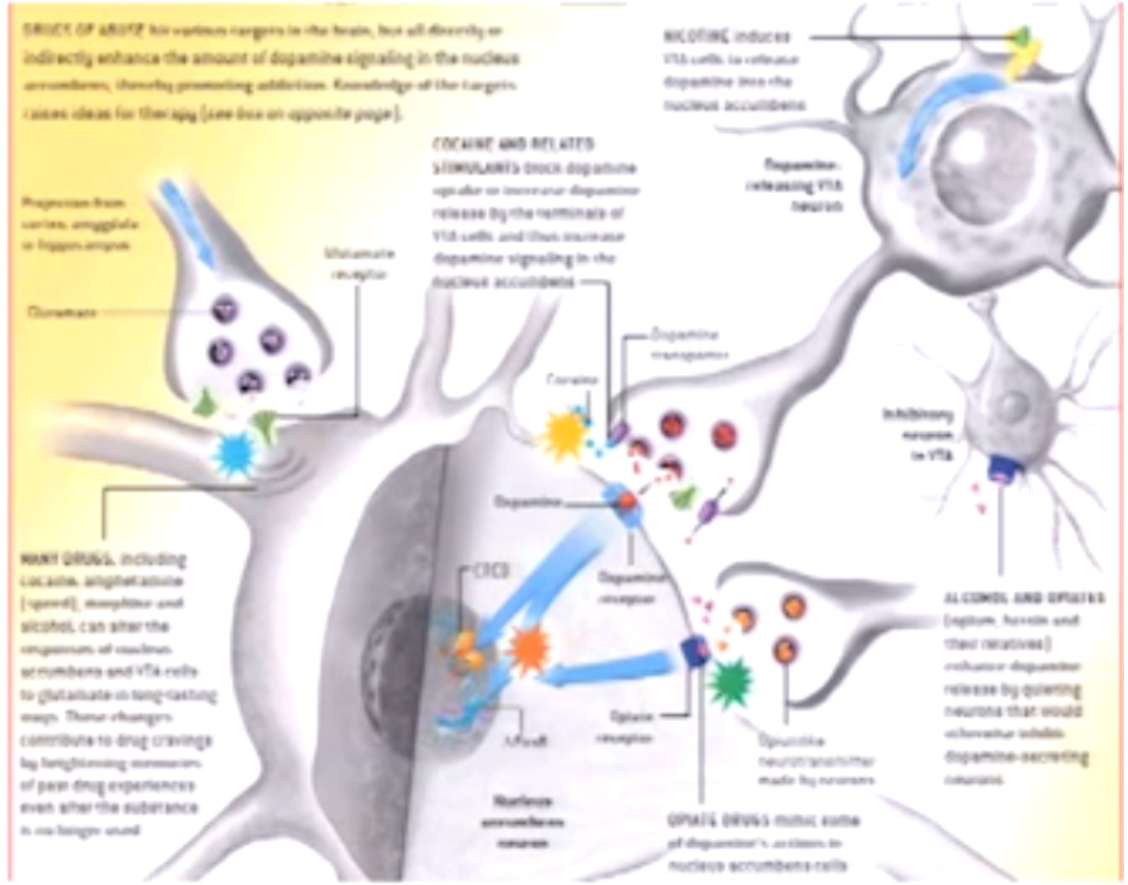


Age at cannabis use disorder as per DSM IV

NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2003.

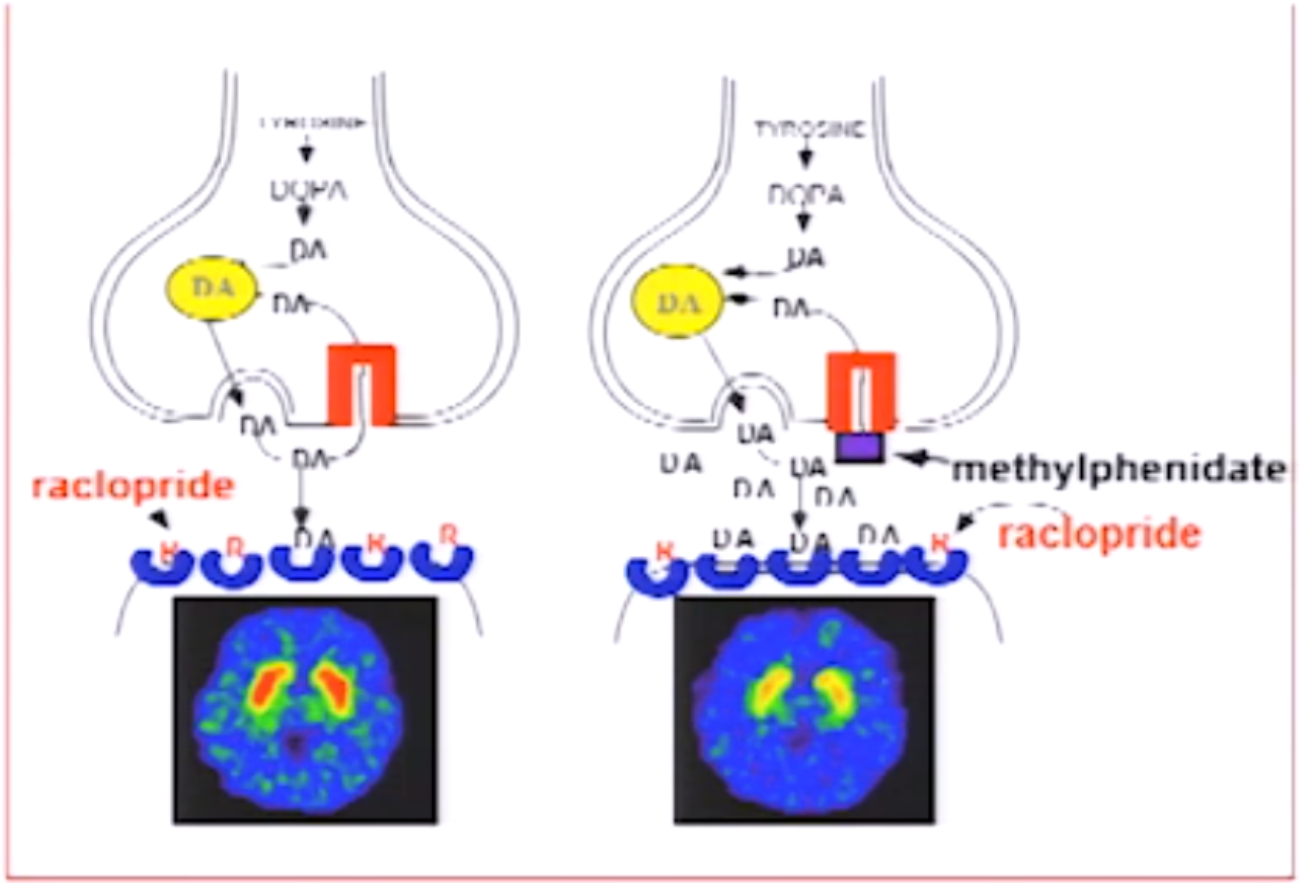
Drugs Increase DA in NAcc, which is Associated with Reward

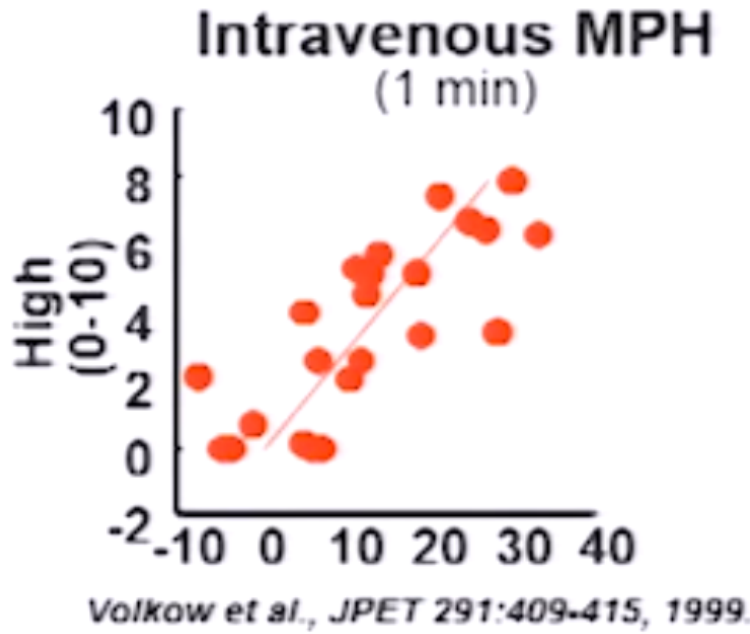




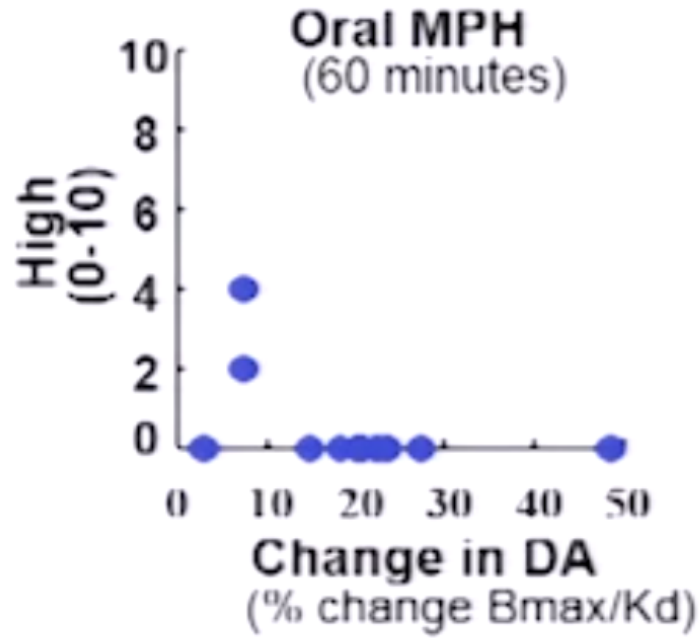
Nestler EJ & Malenka RC. Sci. Amer. March 2004: 78-85.

DA and the Rewarding Effects of Drugs in Humans





Volkow et al., JPET 291:409-415, 1999.



DA increases induced by intravenous but not by oral administration of MPH were associated with the "high" … WHY?

REASON WHY?

- BECOME FREQUENT USER/DEPENDENCE
- SCHIZOPHRENIA
- PSYCHOTIC LIKE REACTION
- LOW INTELLIGENCE
- AND ALSO CB1 (THC) REALLY A BAD GUY IN PSYCHOSIS?

กัญชาและโรคจิต และวิปลาศชั่วขณะ

.

- สืบเนื่องมาจาก บทความใน วารสาร lancet 2019 ที่ติดตามคนใช้กัญชาและพบว่าเกิดโรคจิตมากขึ้น มากขึ้น ต้องอ่านบทบรรณาธิการและอ่านข้อมูลก่อนหน้านั้นว่าการเป็นโรคจิตนั้นมีปัจจัยหลายประการที่เกี่ยวข้อง ได้แก่
- ความโน้มเอียงของบุคคลนั้นที่พร้อมจะเกิดเป็นโรคจิต
- มีความโน้มเอียงที่จะติด มีความโน้มเอียงที่จะต้องใช้บ่อยหรือมีอาการวิปลาสไปชั่วขณะ
- เกิดขึ้นจากการใช้สารปริมาณสูงโดยเฉพาะที่เป็น THC รวมทั้งประเภทที่มาจากการสังเคราะห์

กัญชาและโรคจิต และวิปลาศชั่วขณะ

- นอกจากนั้นรายงานล่าสุดในวารสาร annals of internal medicine วันที่ 26 มีนาคม 2562 พบว่าอาการทางจิตที่เกิดขึ้นหลังการเสพแทนที่จะเกิดจากการสูบ กลับกลายเป็นที่ได้จากการกินหรือหยดใต้ลิ้นจากน้ำมันทั้งนี้เนื่องจากกระบวนการดังกล่าวจะทำให้กัญชาออกฤทธิ์ช้าตั้งแต่หนึ่งถึง 4 ชั่วโมงทำให้ต้องกินหรือหยดซ้ำ ๆ คืออยากให้ออกฤทธิ์เร็วเลยกลายเป็นทำให้ได้ปริมาณสารในขนาดสูงไป และเกิดอาการได้ง่ายขึ้นในคนที่มีความโน้มเอียงอยู่แล้ว
- คนอังกฤษจะเป็นประสาทหลอนกันหมดรึเปล่า หลังจากสูบกันมายาวนาน?

ที่อังกฤษสูบกันทั่วไปและที่ขายกันตามถนนอย่างผิดกฎหมายนั้นคือของดีแบบแรง THC เยอะ อย่างนั้นคนสูบก็ไม่เห็นเป็นอะไร แล้วคนประสาทหลอนหรือจิตเภทส่วนมากก็ไม่เคยสูบกัญชา

กัญชาและโรคจิต และวิปลาศชั่วขณะ

- กลับมาดูในปี 2012 การศึกษาลงใน Nature Translational Psychiatry ศึกษาสาร CBD ว่าจริง ๆแล้ว ตัว CBD นอกจากไปช่วยปรับความเข้มข้นฤทธิ์ของ THC แล้ว มันยังไปเพิ่มความเข้มข้นของสารชื่อ Anandamide ที่มีอยู่ในร่างกายจากการลดการขจัดทำลายออก และสารนี้ที่อธิบายประโยชน์ของ CBD และช่วยลดการเกิดโรคประสาทหลอนไปอีกระดับหนึ่ง
- มิหนำซ้ำคัดค้านความเชื่อที่ว่า กัญชาทำให้เกิดโรคจิตโดยมีกระบวนการพิสูจน์ในการรักษาผู้ป่วยจิตเภท ประการแรกคือ ใช้ยาพิเศษเจาะจงเฉพาะในการต้าน CB1 receptor ในสมอง ไม่ได้ผลในการควบคุมอาการทางโรคจิต
- และประการที่สอง ระดับกัญชาธรรมชาติในน้ำไขสันหลัง anandamide (AEA) ต่ำกว่าปกติในผู้ป่วยเหล่านี้ ยิ่งอาการมากยิ่งมีระดับต่ำมาก ๆ
- ชี้ว่าแท้จริงอาการทางจิตเกิดจากการพร่องกัญชาในตัว การรักษาโดยเพิ่มพลังกัญชาธรรมชาติในร่างกายโดยใช้ **CBD** ได้ผลเท่ากับใช้ยาโรคจิต แต่ไม่มีผลข้างเคียง

กัญชาติดง่ายไหม?

- ก็ติดยากกว่าบุหรี่ แต่ถ้าใช้ต่อเนื่องทุกวันจะมีประมาณ 10% ที่ติดงอมแงม
- ส่วนคนที่ติดถ้าจะเลิกก็หยุดได้เลยแต่ก็จะมีอาการหงุดหงิด อยากกลับไปใช้เหมือนกับบุหรี่ แต่ไม่ถึงกับเป็นอันตราย และข้อดีคือถึงจะใช้เยอะมากก็ไม่ทำให้หยุดหายใจเสียชีวิตเหมือนกับฝิ่นนะ ใช้กัญชาอาจจะมีปัญหาเรื่องความจำและความสามารถของสมองในระยะสั้น พอมันออกจากร่างกาย ซึ่งประมาณ 20 วัน ทุกอย่างก็จะกลับมาเหมือนเดิมไม่มีผลเสียระยะยาว
- ใช้กัญชาแล้วได้ใจ ไปใช้สารเสพติดอื่นที่แรงกว่าเช่นเฮโรอีนไหม ไม่มีหลักฐานว่าจะไปใช้อะไรมากกว่านี้
-

international working group within the framework of the EnhancingNeuro-ImagingGeneticsThroughMeta-Analysis (ENIGMA)project

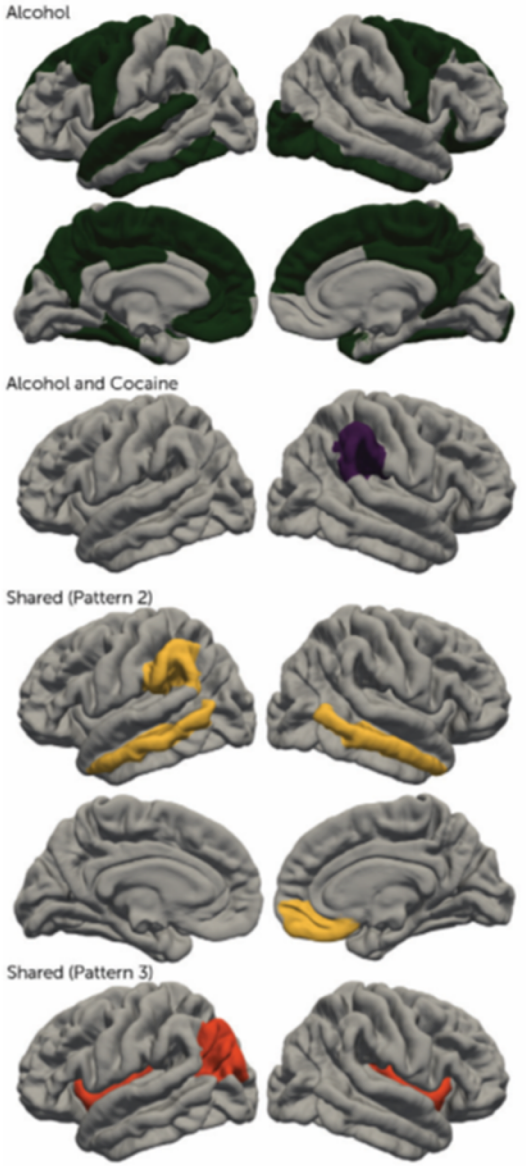
Whether regional differences in brain volume measured by MRI can provide clinically useful biomarkers of substance dependence. Absence of substance-specific linear effects on brain volume related to NICOTINE, METHAMPHETAMINE, OR CANNABIS DEPENDENCE despite the collection of large pooled samples.

ajp.psychiatryonline.org

Mega-Analysis of Gray Matter Volume in Substance Dependence: General and Substance-Specific Regional Effects

Scott Mackey, Ph.D., Nicholas Allgaier, Ph.D., Bader Chaarani, Ph.D., Philip Spechler, B.A., Catherine Orr, Ph.D., Janice Bunn, Ph.D., Nicholas B. Allen, Ph.D., Nelly Alia-Klein, Ph.D., Albert Batalla, M.D., Ph.D., Sara Blaine, Ph.D., Samantha Brooks, Ph.D., Elisabeth Caparelli, Ph.D., Yann Ying Chye, Ph.D., Janna Cousijn, Ph.D., Alain Dagher, M.D., Sylvane Desrivieres, Ph.D., Sarah Feldstein-Ewing, Ph.D., John J. Foxe, Ph.D., Rita Z. Goldstein, Ph.D., Anna E. Goudriaan, Ph.D., Mary M. Heitzeg, Ph.D., Robert Hester, Ph.D., Kent Hutchison, Ph.D., Ozlem Korucuoglu, Ph.D., Chiang-Shan R. Li, M.D., Ph.D., Edythe London, Ph.D., Valentina Lorenzetti, Ph.D., Maartje Luijten, Ph.D., Rocio Martin-Santos, M.D., April May, M.A., Reza Momenan, M.D., Angelica Morales, Ph.D., Martin P. Paulus, M.D., Godfrey Pearlson, M.A., M.B.B.S., Marc-Etienne Rousseau, M.Sc., Betty Jo Salmeron, M.D., Renée Schluter, Ph.D., Lianne Schmaal, Ph.D., Gunter Schumann, M.D., Ph.D., Zsuzsika Sjoerds, Ph.D., Dan J. Stein, Ph.D., Elliot A. Stein, Ph.D., Rajita Sinha, Ph.D., Nadia Solowij, Ph.D., Susan Tapert, Ph.D., Anne Uhlmann, Ph.D., Dick Veltman, M.D., Ph.D., Ruth van Holst, Ph.D., Sarah Whittle, Ph.D., Margaret J. Wright, Ph.D., Murat Yücel, Ph.D., Sheng Zhang, Ph.D., Deborah Yurgelun-Todd, Ph.D., Derrek P. Hibar, Ph.D., Neda Jahanshad, Ph.D., Alan Evans, Ph.D., Paul M. Thompson, Ph.D., David C. Glahn, Ph.D., Patricia Conrod, Ph.D., Hugh Garavan, Ph.D., the ENIGMA Addiction Working Group

FIGURE 1. Cortical Regions of Interest Exhibiting Substance-Specific or Shared Substance-General Effects Displayed on the Surface of Partially Inflated Average Brains[a]



[a] Substance specific: alcohol alone (green), alcohol and cocaine (purple); substance general: pattern 2 (yellow), pattern 3 (orange).

nature neuroscience

ARTICLES

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GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia

Joëlle A. Pasman[1,37], Karin J. H. Verweij[1,2,37], Zachary Gerring[3], Sven Stringer[4], Sandra Sanchez-Roige[5], Jorien L. Treur[6], Abdel Abdellaoui[2], Michel G. Nivard[7], Bart M. L. Baselmans[7], Jue-Sheng Ong[3], Hill F. Ip[7], Matthijs D. van der Zee[7], Meike Bartels[7], Felix R. Day[8], Pierre Fontanillas[9], Sarah L. Elson[9], the 23andMe Research Team[10], Harriet de Wit[11], Lea K. Davis[12], James MacKillop[13], The Substance Use Disorders Working Group of the Psychiatric Genomics Consortium[14], International Cannabis Consortium[15], Jaime L. Derringer[16], Susan J. T. Branje[17], Catharina A. Hartman[18], Andrew C. Heath[19], Pol A. C. van Lier[20], Pamela A. F. Madden[19], Reedik Mägi[21], Wim Meeus[17], Grant W. Montgomery[22], A. J. Oldehinkel[18], Zdenka Pausova[23], Josep A. Ramos-Quiroga[24,25,26,27], Tomas Paus[28,29], Marta Ribases[24,25,26], Jaakko Kaprio[30], Marco P. M. Boks[31], Jordana T. Bell[32], Tim D. Spector[32], Joel Gelernter[33], Dorret I. Boomsma[7], Nicholas G. Martin[3], Stuart MacGregor[3], John R. B. Perry[8], Abraham A. Palmer[5,34], Danielle Posthuma[4], Marcus R. Munafò[6,35], Nathan A. Gillespie[3,36,38], Eske M. Derks[3,38] and Jacqueline M. Vink[1,38*]

Cannabis use is a heritable trait that has been associated with adverse mental health outcomes. In the largest genome-wide association study (GWAS) for lifetime cannabis use to date ($N = 184{,}765$), we identified eight genome-wide significant independent single nucleotide polymorphisms in six regions. All measured genetic variants combined explained 11% of the variance. Gene-based tests revealed 35 significant genes in 16 regions, and S-PrediXcan analyses showed that 21 genes had different expression levels for cannabis users versus nonusers. The strongest finding across the different analyses was CADM2, which has been associated with substance use and risk-taking. Significant genetic correlations were found with 14 of 25 tested substance use and mental health–related traits, including smoking, alcohol use, schizophrenia and risk-taking. Mendelian randomization analysis showed evidence for a causal positive influence of schizophrenia risk on cannabis use. Overall, our study provides new insights into the etiology of cannabis use and its relation with mental health.

2,387 cases and almost 50,000 controls, plus a replication sample of 5,501 cases and ~300,000 controls.

2016 International Cannabis Consortium (ICC) and is based on a sample size of 32,330 individuals in the discovery sample along with 5,627 individuals in the replication sample

four genes significantly associated with lifetime cannabis use: NCAM1, CADM2, SCOC and KCNT2

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JAMA Psychiatry | Original Investigation

Genetic Predisposition vs Individual-Specific Processes in the Association Between Psychotic-like Experiences and Cannabis Use

Psychotic-like

Nicole R. Karcher, PhD; Deanna M. Barch, PhD; Catherine H. Demers, MA; David A. A. Baranger, PhD; Andrew C. Heath, PhD; Michael T. Lynskey, PhD; Arpana Agrawal, PhD

CONCLUSIONS AND RELEVANCE Despite the strong contribution of shared genetic factors, frequent and problem cannabis use also appears to be associated with PLEs via person-specific pathways. This study's findings suggest that policy discussions surrounding legalization should consider the influence of escalations in cannabis use on traitlike indices of vulnerability, such as PLEs, which could contribute to pervasive psychological and interpersonal burden.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2018.2546
Published online October 17, 2018.

HUMAN CONNECTOME PROJECT (1188) AND THE AUSTRALIAN TWIN REGISTRY COHORT 3 (ATR3)(3486)

- frequent use(ie,>100times), a DSM-IV lifetime cannabis use disorder diagnosis, and current cannabis use.
- Genetic and environmental correlation s between cannabis involvement and PLEs were estimated. Generalized linear mixed models examined PLE differences in twin and nontwin sibling pairs discordant for cannabis use.
- RESULTS
- Psychotic-like experiences were associated with frequent cannabis use(β=0.11;95%CI,0.08-0.14),cannabis use disorder(β=0.13;95%CI, 0.09-0.16),and current cannabis use(β=0.07;95%CI,0.04-0.10) even after adjustment for covariates.
- Correlated genetic factors explained between **69.2% and 84.1%** of this observed association. Within discordant pairs of twins/siblings(Npairs,308-324),Psychotic-like experiences were more common in cannabis-exposed individuals compared with their relative who used cannabis to a lesser degree

Citation: Transl Psychiatry (2012) 2, e94, doi:10.1038/tp.2012.15

www.nature.com/tp

Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia

FM Leweke[1,2], D Piomelli[3,4], F Pahlisch[1,3], D Muhl[2,3], CW Gerth[2], C Hoyer[1,2], J Klosterkötter[2], M Hellmich[5] and D Koethe[1,2]

Cannabidiol is a component of marijuana that does not activate cannabinoid receptors, but moderately inhibits the degradation of the endocannabinoid anandamide. We previously reported that an elevation of anandamide levels in cerebrospinal fluid inversely correlated to psychotic symptoms. Furthermore, enhanced anandamide signaling let to a lower transition rate from initial prodromal states into frank psychosis as well as postponed transition. In our translational approach, we performed a double-blind, randomized clinical trial of cannabidiol vs amisulpride, a potent antipsychotic, in acute schizophrenia to evaluate the clinical relevance of our initial findings. Either treatment was safe and led to significant clinical improvement, but cannabidiol displayed a markedly superior side-effect profile. Moreover, cannabidiol treatment was accompanied by a significant increase in serum anandamide levels, which was significantly associated with clinical improvement. The results suggest that inhibition of anandamide deactivation may contribute to the antipsychotic effects of cannabidiol potentially representing a completely new mechanism in the treatment of schizophrenia.
Translational Psychiatry (2012) **2,** e94; doi:10.1038/tp.2012.15; published online 20 March 2012

The search for safe and effective drugs to treat schizophrenia is hindered by the complex nature of this disorder, which is known to involve multiple brain neurotransmitters.[1] Among them are the endogenous cannabinoids, a family of lipid messengers that target the same cell surface receptors engaged by Δ^9-tetrahydrocannabinol in marijuana.[2] Because Δ^9-tetrahydrocannabinol and other direct-acting cannabinoid agonists can induce psychotic symptoms both in healthy volunteers[3–5] and schizophrenic patients,[6,7] it has been suggested that hyperactivity of the endocannabinoid system might contribute to psychotic states.[8,9] This idea has fueled two large-scale clinical trials with CB_1-type cannabinoid receptor antagonists in schizophrenia, which yielded, however, negative results.[10,11] A diametrically opposite view — namely that certain components of the endocannabinoid system might have a protective role in schizophrenia — was suggested by studies with antipsychotic-naïve schizophrenic patients, in which it was found that the symptom intensity experienced by these subjects was negatively correlated with cerebrospinal levels of anandamide,[12,13] an endocannabinoid transmitter known to be involved in the regulation of pain, mood and cognition.[14] Consistent with these clinical observations, animal experiments have shown that pharmacological blockade of anandamide degradation attenuates, rather than enhances, psychotic-like behaviors induced in rodents by amphetamine and phencyclidine.[15,16]

affinity[17,18] and is devoid of overt cannabimimetic or pro-psychotic properties.[17] Biochemical studies indicate that cannabidiol may enhance endogenous anandamide signaling indirectly, by inhibiting the intracellular degradation of anandamide catalyzed by the enzyme fatty acid amide hydrolase (FAAH).[19] Furthermore, preliminary clinical case reports suggest that cannabidiol might exert antipsychotic effects in schizophrenic patients.[20–22] In addition, experimental studies show that cannabidiol reduces psychosis-like effects of Δ^9-tetrahydrocannabinol and synthetic analogs.[22,23]

ความเชื่อที่ว่า กัญชาทำให้เกิดโรคจิต จริงหรือ?

1- การต้าน CB1 receptor ในผู้ป่วยจิตเภท ไม่ได้ผล

2- ระดับกัญชาธรรมชาติในน้ำไขสันหลัง anandamide (AEA) ต่ำกว่าปกติ ชี้ว่าแท้จริงอาการทางจิตเกิดจากการพร่องกัญชาในตัว

การรักษาโดยเพิ่มพลังกัญชาธรรมชาติในร่างกาย ได้ผลเท่ากับใช้ยาโรคจิต แต่ไม่มีผลข้างเคียง

the presence of baseline differences before marijuana involvement, the lack of a dose–response relationship, and an absence of meaningful differences between discordant siblings lead us to conclude that the deficits observed in marijuana users are attributable to confounding factors that influence both substance initiation and IQ rather than a neurotoxic effect of marijuana.

www.pnas.org/cgi/doi/10.1073/pnas.1516648113

Significance

Marijuana is the most commonly used recreational drug in the United States. Some studies suggest that marijuana use in adolescence is linked to declines in intellectual functioning. Because of the infeasibility of studying this phenomenon experimentally, it is unclear whether the association can be causally attributed to marijuana use itself or is instead the result of confounding factors. We approach this issue quasiexperimentally using longitudinal samples of adolescent twins. Among twin pairs discordant for marijuana use, we assessed intelligence quotient (IQ) score changes while adjusting for the effects of genetic influences and other factors shared by members of the same twin pair. Results suggest that familial confounds underlie the association between adolescent marijuana use and declining IQ scores.

Impact of adolescent marijuana use on intelligence: Results from two longitudinal twin studies

Nicholas J. Jackson[a,b,1], Joshua D. Isen[c,1,2], Rubin Khoddam[a], Daniel Irons[c], Catherine Tuvblad[a,d], William G. Iacono[c], Matt McGue[c], Adrian Raine[e,f,g], and Laura A. Baker[a]

[a]Department of Psychology, University of Southern California, Los Angeles, CA 90089; [b]Department of Medicine Statistics Core, University of California, Los Angeles, CA 90024; [c]Department of Psychology, University of Minnesota, Minneapolis, MN 55455; [d]School of Law, Psychology and Social Work, Örebro University, 702 81 Örebro, Sweden; [e]Department of Criminology, University of Pennsylvania, Philadelphia, PA 19104; [f]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104; and [g]Department of Psychology, University of Pennsylvania, Philadelphia, PA 19104

CANNABIDIOL (CBD)

Pre-Review Report

Agenda Item 5.2

Expert Committee on Drug Dependence
Thirty-ninth Meeting
Geneva, 6-10 November 2017

World Health Organization

Contents

เจ๋ง clinical and scientific evidence 2017

TOTALITY OF EVIDENCE

WHO THC Sept 2018 only clinical trials

Original Articles and Reviews

Human Thriving

A Conceptual Debate and Literature Review

Daniel J. Brown,[1] Rachel Arnold,[1] David Fletcher,[2] and Martyn Standage[1]

[1]Department for Health, University of Bath, UK
[2]School of Sport, Exercise, and Health Sciences, Loughborough University, UK

Abstract: Human beings have an inherent drive for self-improvement and growth (Maslow, 1965; Ryan & Deci, 2002). In a quest to understand how human beings achieve fulfillment, researchers have sought to explain why some individuals thrive in certain situations, whereas others merely survive or succumb. The topic of thriving has become popular with scholars, resulting in a divergent body of literature and a lack of consensus on the key processes that underpin the construct. In view of such differences, the purpose of this paper is threefold: (i) to review a number of existing theoretical and conceptual debates, and to propose a conceptualization of thriving applicable across different populations and domains; (ii) to consolidate pertinent bodies of extant thriving research and identify key personal and contextual enablers to inform applied practice; and (iii) to identify noteworthy gaps within existing literature so as to make recommendations for future research and, ultimately, support the development of effective psychosocial interventions for thriving.

Keywords: functioning, health, performance, thrive, well-being

OPEN

Citation: Transl Psychiatry (2016) **6**, e905; doi:10.1038/tp.2016.169

www.nature.com/tp

REVIEW

Endocannabinoid signaling in social functioning: an RDoC perspective

DS Karhson[1,2], AY Hardan[2] and KJ Parker[2]

Core deficits in social functioning are associated with various neuropsychiatric and neurodevelopmental disorders, yet biomarker identification and the development of effective pharmacological interventions has been limited. Recent data suggest the intriguing possibility that endogenous cannabinoids, a class of lipid neuromodulators generally implicated in the regulation of neurotransmitter release, may contribute to species-typical social functioning. Systematic study of the endogenous cannabinoid signaling could, therefore, yield novel approaches to understand the neurobiological underpinnings of atypical social functioning. This article provides a critical review of the major components of the endogenous cannabinoid system (for example, primary receptors and effectors—Δ9-tetrahydrocannabinol, cannabidiol, anandamide and 2-arachidonoylglycerol) and the contributions of cannabinoid signaling to social functioning. Data are evaluated in the context of Research Domain Criteria constructs (for example, anxiety, chronic stress, reward learning, motivation, declarative and working memory, affiliation and attachment, and social communication) to enable interrogation of endogenous cannabinoid signaling in social functioning across diagnostic categories. The empirical evidence reviewed strongly supports the role for dysregulated cannabinoid signaling in the pathophysiology of social functioning deficits observed in brain disorders, such as autism spectrum disorder, schizophrenia, major depressive disorder, posttraumatic stress disorder and bipolar disorder. Moreover, these findings indicate that the endogenous cannabinoid system holds exceptional promise as a biological marker of, and potential treatment target for, neuropsychiatric and neurodevelopmental disorders characterized by impairments in social functioning.

Translational Psychiatry (2016) **6,** e905; doi:10.1038/tp.2016.169; published online 27 September 2016

Endocannabinoid system and human thriving behavior

- Mind-body-soul
- Cognitive neuroscience
- Translate to all aspects in cultural/business/governing management
- Brainwash

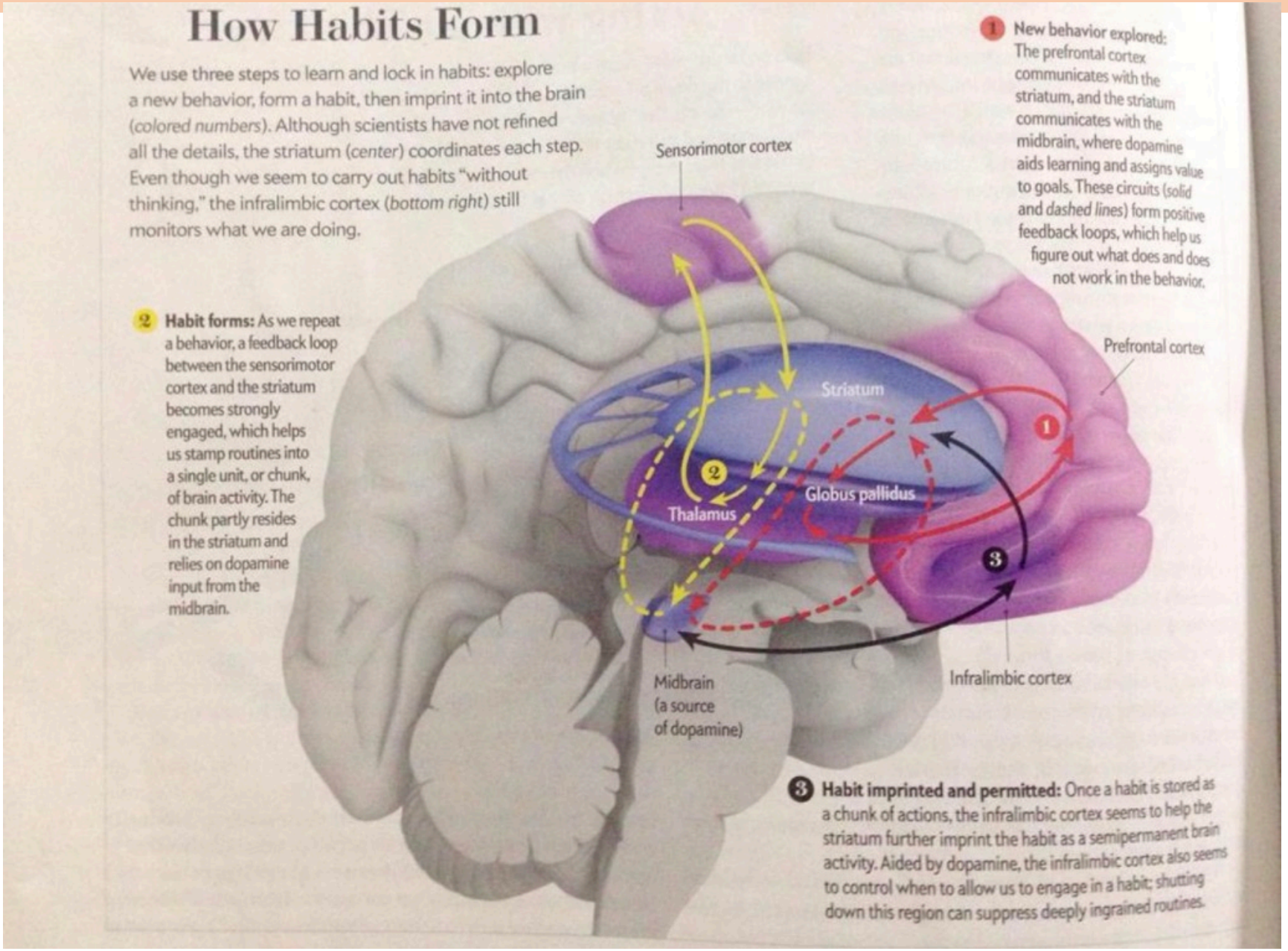
Disgust เป็นศัพท์วิทยาศาสตร์ทางสมองและอารมณ์

- ในระยะแรกจัดเป็นอารมณ์ความรู้สึกที่มีต่อการรับรู้สิ่งสกปรก สิ่งผิดปกติ จากประสาทสัมผัส ทั้งรส รูป กลิ่น และมีการบันทึกเป็นหนังสือโดย ชาร์ลส์ ดาร์วิน (Charles Darwin) ตั้งแต่ปี ค.ศ.1872 และในเวลาต่อมา **Robert Plutchik (**เสียชีวิตเมื่ออายุ 78, 29 เมษายน 2006) ถือว่า
- "สะอิดสะเอียน" จัดเป็นอารมณ์ความรู้สึก 1ใน 8 อย่าง ได้แก่ ความโกรธ (**Anger)** กลัว (**Fear)** เศร้าสร้อย (**Sadness)** สะอิดสะเอียน (**Disgust)** ประหลาดใจ (**Surprise)** ความอยากรู้อยากเห็น (**Curiosity)** การยอมรับ (**Acceptance)** และ ความปิติ (**Joy)**
- **Plutchik** ได้เสนอว่า อารมณ์ความรู้สึกเหล่านี้เป็นการตอบสนองขั้นพื้นฐาน ซึ่งจะมีการพัฒนาขึ้นเรื่อย ๆเพื่อให้คนสามารถปรับตัวให้เข้ากับสภาวะแวดล้อม เพื่อมีการดำรงชีวิตอยู่ได้ในสังคม และจรรโลงสังคมในทางที่ถูกต้อง เหมาะสม
- ความสะอิดสะเอียนก่อให้เกิดการเปลี่ยนแปลงของสีหน้า (ซึ่งสีหน้าสามารถจำแนกได้ถึง 15 แบบ ตามทฤษฎีของ **Paul Ekman)** โดยที่จะมีหัวใจเต้นช้าลง ซึ่งต่างจากปฏิกิริยาของหัวใจที่เต้นเร็วขึ้นในอารมณ์กลัว หรือโกรธ
- ดังนั้น "สะอิดสะเอียน" ขณะนี้ในปัจจุบันไม่ได้จำกัดว่าเป็นความรู้สึก หรือสัญชาติญาณ เพื่อป้องกันชีวิตแต่อย่างเดียว (เช่น มีต่ออาหารที่เป็นพิษ สิ่งปฏิกูล อาหารบูด เน่าเสีย ของเสีย) แต่เป็นสัญชาติญาณ อารมณ์ ความรู้สึกที่มีปฏิกิริยา ต่อความไม่ถูกต้องทางศีลธรรม ความไม่ถูกต้องของสังคม ต่อความประพฤติเลวร้าย ซึ่งรวมถึงการย่ำยีผู้ไม่มีทางสู้ ผู้ด้อยโอกาส
- ความ "สะอิดสะเอียน" ก่อให้เกิดความรู้สึก "ละอาย" ต่อพฤติกรรม ความประพฤติที่ผิดมิชอบ ไม่ว่าจะเป็นที่ผู้อื่นก่อขึ้น หรือเป็นจากที่ตนเองก่อก็ตาม
- สมองที่มีส่วนใน "สะอิดสะเอียน" อยู่ที่ **anterior insula (Nature, 1997)** จากการศึกษาโดยคอมพิวเตอร์สนามแม่เหล็กไฟฟ้า (**Functional magnetic resonance imaging)** แต่ยังมีข้อโต้แย้งในตำแหน่งของสมองส่วนนี้บ้าง (**Neuroreport, 2002; Neuroimage, 2004)** ผู้ป่วยที่มีสมองผิดปกติทางกรรมพันธุ์ (**Huntington's disease)** ปรากฏว่าไม่มีปฏิกริยาของความ "สะอิดสะเอียน" ต่อการรับรู้ทางวัตถุสิ่งของหรือทางการรับรส โดยที่มีความเสื่อมของสมองเป็นคนละส่วนกันกับ **anterior insula**

ความประพฤติ...นิสัย...มันจะเปลี่ยนกันได้ไหม?

- กว่าจะเกิดเป็นนิสัย เกิดการติดขึ้นมาได้ จะต้องมีขั้นตอน กระบวนการจารึกเข้าไปในสมองส่วนจำเพาะ คนที่ติดการพนันจะมีปฏิกิริยาโต้ตอบต่อผลของการแพ้ชนะต่างกับคนทั่วไป โดยที่คนติดหวยเมื่อผลออกมาเฉียดฉิวจะรู้สึกว่า เนี่ย...ถ้าตีเลข ตีฝันดีอีกสักนิดงวดหน้าคุ้มถูกแน่ ทั้งๆ ที่เสียเงินไปแล้วก็ตาม แต่คนปกติ “เสีย” ก็คือ “เสีย” และเกิดความสำนึก “เฮ้ย...เสียเยอะเลิกเล่นดีกว่า”
- ที่ว่ามีส่วนสมองจำเพาะทำให้ติดย้ำทำอยู่เดิมๆ มีตัวอย่างให้เห็นในปี 2008 ที่ศาลสั่งให้บริษัทยาจ่ายเงินเป็นจำนวน 8.2 ล้านเหรียญ แก่คนที่เสียพนันไป 250,000 เหรียญ เพราะยาที่ใช้ทำให้มีสารเคมีที่เฉพาะเจาะจงต่อสมองที่ยื่อที่จะทำเช่นนั้นตลอด
- กว่าที่จะเกิดเป็นนิสัย (สันดาน) ได้จะเริ่มด้วยการฟอร์มความประพฤติก่อน โดยสมองส่วนหน้า **Prefrontal Cortex** จะมีสัญญาณต่อกับสมองล้ำลงไปส่วน **Striatum** ซึ่งต่อกับก้านสมองส่วนตัน **Midbrain** จากวงจรแรกนี้จะปรับตัวเองว่าควรจะมีรูปแบบการประพฤติแบบไหนที่เวิร์คสุด และเมื่อลองประพฤติซ้ำในรูปแบบดังกล่าวบ่อยขึ้น จะเกิดวงจรที่ 2 ระหว่าง **Striatum** ของวงจร ที่1 ต่อกับสมอง **Sensorimotor** และต่อไปจะเริ่มจดบันทึกลงใน **Striatum** ซึ่งมีสาร **Dopamine** จาก **Midbrain** คอยตอกย้ำ
- วงจรที่ 3 คราวนี้จะเป็นการถาวร โดยวงจร 2 จะมีสมองอารมณ์พฤติกรรม **Infralimbic Cortex** เพื่อจารึกนิสัยให้เป็นสันดานติดทนใน **Striatum** ทั้งนี้โดยสาร **Dopamine** เป็นตัวส่งเช่นเดิม เกิดเป็นสันดานมีพฤติกรรมซ้ำซาก
- การดัดสันดานต้องทำการกดเนื้อสมองที่ถูกจารึกไปแล้วไม่ให้เป็นตัวครอบครองกำหนดพฤติกรรม
- ข้อมูลเหล่านี้ออกมาปรากฏประมาณปี 2012 และทำให้เป็นครรลองของความประพฤติ ยกตัวอย่างง่ายๆเช่น จะกลับบ้านทางไหน ถนนไหน การที่ไม่สามารถเปลี่ยนจากครรลองเดิมได้จะเป็นสันดานหรือเช่นการติดสารเสพติด ติดรูปแบบการกระทำที่แม้จะเลวแสนเลวก็เปลี่ยนไม่ได้และรวมไปถึงการติดเหล้า ติดบุหรี่
- ในรายงานของปี 2017 วงจรสันดานอาจมีความกว้างขวางขึ้นใน **Orbitofronal Cortex (OFC)** ซึ่งเป็นวงจรสมองของการตัดสินใจโดยมีสารเคมีคล้ายกับกัญชาเกิดขึ้นตามธรรมชาติในสมองหรือ Endocannabinoids เข้ามาเกียวข้อง
- สารกัญชาในสมองตามธรรมชาตินี้มีส่วนในความเจริญอาหาร ความเจ็บปวด อารมณ์ และความจำ และผลสุขจากกัญชา
- การทดลองปิดระบบวงจรนี้มีผลทำให้คงทำตามสันดานเดิมไม่สามารถปรับเปลี่ยนไปให้มีพฤติกรรม ความประพฤติ การกระทำอย่างอื่น โดย Endocannabinoids นี้อาจจะเป็นตัวสำคัญอีกตัวหนึ่งที่กดการทำงานของสมอง OFC ที่จะส่งสัญญาณไปหา Dorsomedial Sriatum
- เช่นถ้าปิดวงจรนี้จะกลับบ้านด้วยทางซ้ำซาก แม้รถจะติดแสนสาห้ส นักท่วม
- การทดลองในหนูซึ่งขจัดตัวรับสัญญาณ Endocannabinoid Type 1 receptor ทำให้หนูมีทางเลือกที่จะปฏิบัติซ้ำซาก หรือเลือกวิธีปฏิบัติใหม่ที่สมเหตุสมผลกว่า
- คนที่ฆ่าคน โจรกรรม ข่มขืน ซ้ำซาก จะรอให้มีการผลิตยาซึ่งในคนรออีกชาติหน้าในการลบสันดานในวงจรที่ 3 และใน OFC ได้ การเกิดสันดานเป็นกระบวนการต่อเนื่องเพาะบ่มผ่านการคัดกรองการกระทำและซ้ำซาก เป็นนิสัยที่แก้ไม่หาย คนที่โกงคอร์รัปชั่นเป็นอีกตัวอย่าง โดยเก่ไปกว่านั้นที่ “ตอแหล” ว่าโกงโดยสุจริต คงไม่ต้องตัดสมองบางส่วนในพวกนี้ ตัดทั้งหัวน่าจะเป็นทางออกและวิธีที่ดีที่สุด ที่ทุกคนยอมรับได้

ความประพฤติ นิสัย สันดาน



eCB SIGNALING AND NEGATIVE VALENCE SYSTEMS

ANXIETY

FEAR

STRESS

eCB SIGNALING AND POSITIVE VALENCE SYSTEMS

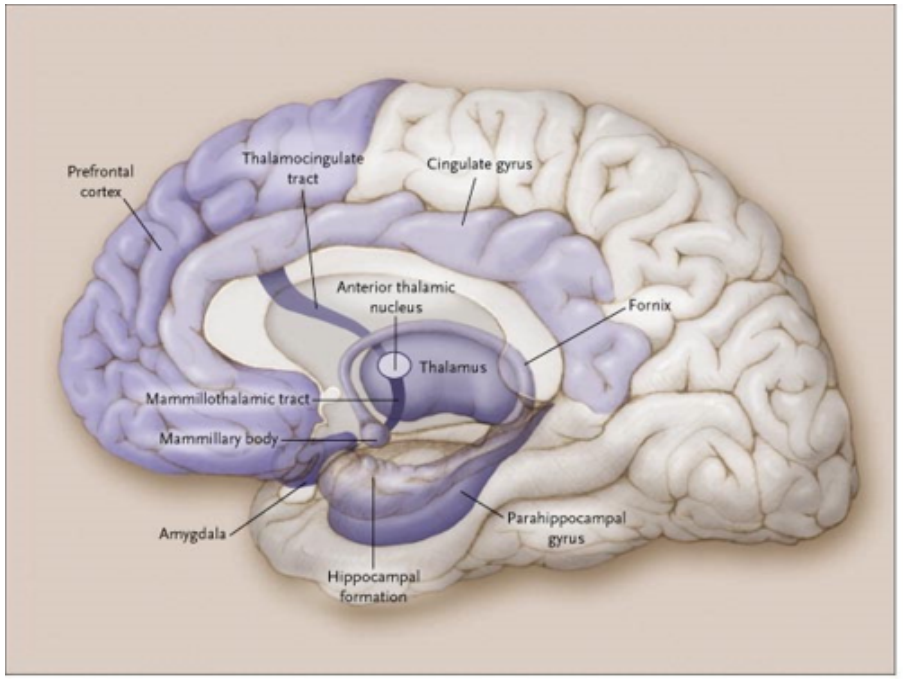
Reward learning
Social motivation

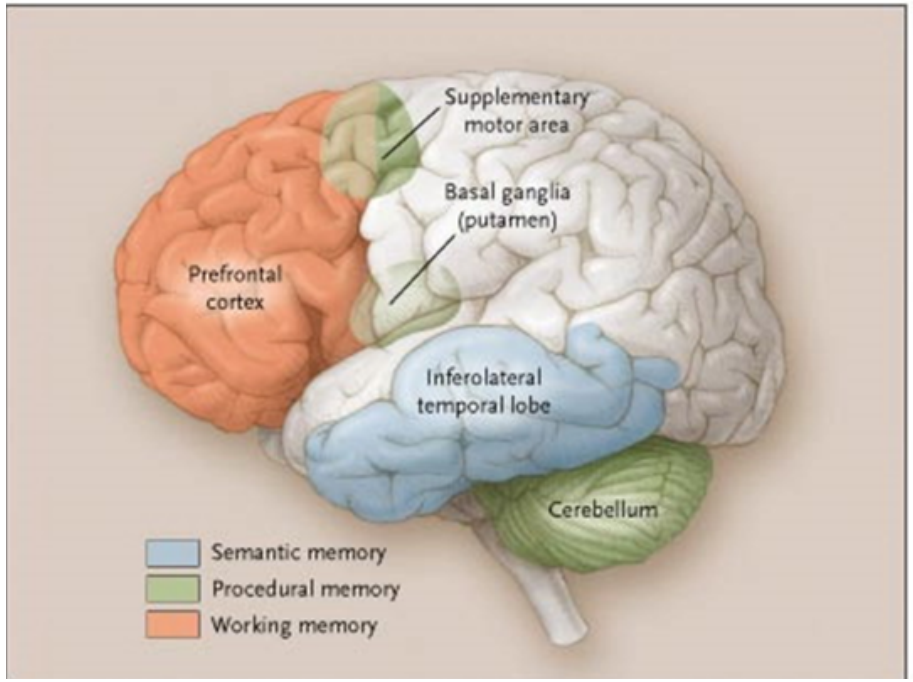
eCB SIGNALING AND COGNITIVE SYSTEMS

- **Declarative memory**
  (encoding, consolidation, storage and retrieval of factual information) supports social interactions by providing biographical and episodic recall.
- as a store of experience-outcomes and integrates previous conclusions with new input, as well as emotion, motivation and perception
- **Working memory**

Memory System	Major Anatomical Structures Involved	Length of Storage of Memory	Type of Awareness	Examples
Episodic memory	Medial temporal lobes, anterior thalamic nucleus, mammillary body, fornix, prefrontal cortex	Minutes to years	Explicit, declarative	Remembering a short story, what you had for dinner last night, and what you did on your last birthday
Semantic memory	Inferolateral temporal lobes	Minutes to years	Explicit, declarative	Knowing who was the first president of the United States, the color of a lion, and how a fork differs from a comb
Procedural memory	Basal ganglia, cerebellum, supplementary motor area	Minutes to years	Explicit or implicit, nondeclarative	Driving a car with a standard transmission (explicit) and learning the sequence of numbers on a touch-tone phone without trying (implicit)
Working memory	Phonologic: prefrontal cortex, Broca's area, Wernicke's area Spatial: prefrontal cortex, visual-association areas	Seconds to minutes; information actively rehearsed or manipulated	Explicit, declarative	Phonologic: keeping a phone number "in your head" before dialing Spatial: mentally following a route or rotating an object in your mind

NEJM 2005





eCB SIGNALING AND SOCIAL PROCESSING SYSTEMS

- Affiliation and attachment
  - Maternal-fetus-infant
- Social communication

Table 1. Endocannabinoid system component in RDoC domains

RDoC construct	*Mediating circuit*	*CB1R in circuitry*	*CB2R in circuitry*	*2-AG*	*AEA*
Anxiety	Interpret: BNST, HPC, amygdala Evaluate and response initiation: PFC, NAc, VTA, hypothalamus[28,29]	BNST[a], [a]HPC, amygdala, [a]PFC, [a]NAc medium spiny neurons, hypothalamus[a,5,8,18]	Microglia,[30] VTA and NAc dopaminergic neurons[16,31]	↑in brain → anxiolytic[30]	↓in brain → anxiogenic[30]
Chronic stress	HPA, amygdala–medial PFC–striatum[32–34]	[a]PFC, [a]HPC, [a]NAc, amygdala, HPA[a,19,35]	Rats: amygdala, HPC, PFC, hypothalamus[25]	Amygdalar impairment in synthesis,[30] ↑in PFC[36]	↓in amygdala (via↑FAAH)[30]
Motivation	Orbitofrontal cortex, amygdala, VTA, NAc[37–39]	Amygdala, [a]HPC, VTA and [a]NAc dopaminergic neurons[38,40,41]	VTA dopaminergic neurons[31,40]	↑in NAc → ↑ dopamine[38,41,42]	↑in NAc → ↑dopamine
Reward learning	VTA, NAc, PFC, hypothalamus, amygdala[40,42]	[a]NAc medium spiny neurons, [a]HPC, amygdala, VTA and [a]NAc dopaminergic neurons, hypothalamus[a], [a]PFC[40,42,43]	VTA dopaminergic neurons[31]	↑in NAc → ↑ dopamine[38,41,42]	↑in NAc → ↑dopamine
Declarative memory	PFC, amygdala, HPC (dentate gyrus, CA1, CA3), VTA, NAc[44]	[a]PFC, amygdala, GABAergic interneurons, [a]HPC (dentate gyrus, CA1 and CA3).[18,19]	HPC interneuron cholecystokinin (+) basket cells[45]	↓HPC CB1R binding → ↑GABA [45,46]	HPC [18]↑(via ↓FAAH) → ↑acquisition[47,48]
Working memory	PFC–parietal–cingulate–thalamus–NAc, HPC[49,50]	[a]NAc medium spiny neuron, GABAergic hippocampal interneurons[46]	HPC[23]	↑HPC CB2R binding → ↓encoding/consolidation[51]	↑ (via ↓FAAH) → ↑acquisition[47,48]
Affiliation and attachment	Amygdala, VTA, NAc, PVN, SON, HPA, BNST[52–54]	PVN,[34] SON,[55] HPA,[a,13] BNST[a], amygdala, NAc[12,56]	HPC[23,56]	↑in HPC → ↓ care[54,57] ↑in amygdala → ↓play[36]	Play: ↑amygdala and NAc[12,36]
Social communication	Amygdala, NAc, orbitofrontal cortex, cortico–basal ganglia–thalamo network[58]	HPC, amygdala, NAc [59,60]	Not yet known	Not yet known	↑ (via ↓FAAH) → ↑USVs[61–63]

Abbreviations: AEA, anandamide; 2-AG, 2-arachidonoylglycerol; BNST, bed nucleus of the stria terminalis; FAAH, fatty acid amide hydrolase; GABA, glutamate and γ-aminobutyric acid; HPA, hypothalamus–pituitary–adrenal gland axis; HPC, hippocampus; NAc, nucleus accumbens; PFC, prefrontal cortex; PVN, paraventricular nucleus; RDoC, Research Domain Criteria; SON, supraoptic nucleus; USV, ultrasonic vocalization; VTA, ventral tegmental area. CB1R is the most abundant G-protein-coupled receptor ([a]highest levels/densities, [b]lowest) in the mammalian brain, contributing to cannabinergic effects on 'movement, affective responding, cognition, temperature, appetite and neuroendocrine function'.[8,18] Human mRNA expression for a CB2R isoform has been found in amygdala, striatum, HPC, cortex and cerebellum,[25] with rodents showing additional expression in the cerebral cortex, brain stem, thalamic nuclei and periaqueductal grey.[64] AEA binding elicits sub-maximal receptor signaling, whereas 2-AG binds with much greater efficacy,[42] necessary to produce robust phasic signaling responses.

มูลนิธิข้าวขวัญ

- ไม่ใช่อยู่ที่น้ำมันกัญชา
- ไม่ใช่อยู่ที่ตัวเองว่าเก่ง
- ไม่ใช่ต้องการ ลาภ ยศ สรรเสริญ
- ยอมเสียสละ
- ทำเพื่อใคร
- และนำไปสู่กระบวนการพัฒนาจิตใจ กาย วิญญาณ
- **Endocannabinoid to phytocannabinoid and vice versa**

คุณภาพชีวิต-ป้องกัน-รักษา-ชะลอ
FOR MEDICAL USE

- ***1-อาการแข็งเกร็ง*** *ที่อาจร่วมกับการบิดของกล้ามเนื้อที่เกิดจากความผิดปกติของสมอง ยกตัวอย่างเช่นที่เกิดจากเส้นเลือดตันหรือแตก ความผิดปกติที่ระดับของไขสันหลัง และรวมถึงความผิดปกติที่เกิดขึ้นกับเด็กหลังคลอดที่มีสมองพิการหรือเจริญเติบโตผิดปกติ และโรค**multiple sclerosis***
- ***2-อาการปวดทรมาน*** *ที่นอกเหนือจากมะเร็งหรือปวดจากความผิดปกติของเส้นประสาทหรือระบบประสาท. ยกตัวอย่างเช่นอาการปวดที่เกี่ยวเนื่องจากการอักเสบของข้อ เส้นเอ็นและกล้ามเนื้อซึ่งโดยปรกติจะต้องใช้ยาแก้ปวดอย่างรุนแรงและร่วมกับยาแก้ปวดที่เป็นอนุพันธ์ของมอร์ฟีน*
- ***3-ภาวะของการปฏิเสธอาหาร****ทั้งที่เกิดขึ้นจากโรคทางจิตประสาท* ***anorexia nervosa*** *และโรคทางกายที่เกิดขึ้นที่มีผลกระทบกับจิตใจ และอาการอาเจียนจากเคมีบำบัด*
- ***4-โรคทางสมองได้แก่โรคพาร์กินสันส์และโรคสมองเสื่อมเช่นอัลไซเมอร์ ในทางป้องกัน การชะลอโรค และการบรรเทาอาการ agitation/restlessness****ที่มีอยู่*
- ***5-โรคลมชักทั้งในเด็กและผู้ใหญ่ที่ไม่สามารถคุมด้วยยากันชักหนึ่งชนิด***
- ***6-****โรคจิต****schizophrenia*** ***หรือโรคจิตเภท***
- ***7-****มะเร็ง เป็นยาประกบ เพื่อคุณภาพชีวิต และแก้ไขการเจ็บปวดทรมาน*